

*Novel Insights
into the Treatment of
Complicated Diverticulitis*

Daniël P. V. Lambrichts

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Printing: ProefschriftMaken || www.proefschriftmaken.nl

The printing of this thesis was financially supported by: Department of Surgery Erasmus University Medical Center, Erasmus Universiteit Rotterdam, ChipSoft B.V.

ISBN 978-94-6380-973-3

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Novel Insights into the Treatment of Complicated Diverticulitis

Nieuwe inzichten in de behandeling van
gecompliceerde diverticulitis

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

28 oktober 2020 om 13.30 uur

door

Daniël Peter Valentin Lambrichts
geboren te Brunssum

Promotiecommissie:

Promotoren:

Prof. dr. J.F. Lange

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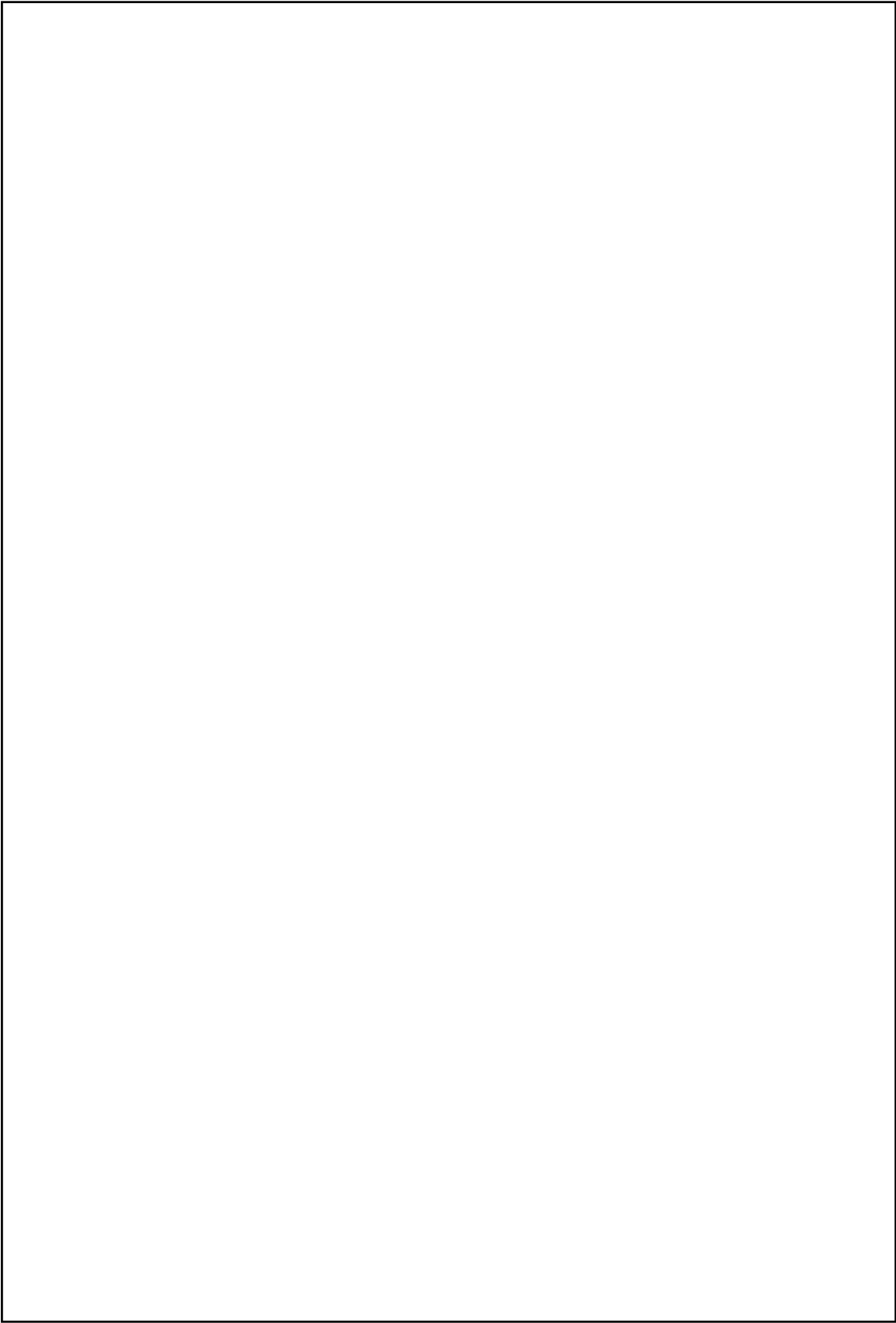
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Chapter 1

General Introduction

Diverticulosis

Diverticulosis is defined as the presence of diverticula in the colonic wall. These diverticula are protrusions of the colonic wall and mostly occur between the antimesenteric and mesenteric taeniae, where blood vessels penetrate the colonic wall. Strictly, these diverticula should be considered as 'false' or 'pseudo' diverticula, as not all bowel wall layers are involved, but only mucosa and submucosa (1-4).

In the Western world, diverticulosis is common and its prevalence increases with age. Investigating prevalence rates of diverticulosis is challenging as the majority of individuals remain asymptomatic. Nevertheless, diverticulosis is estimated to be present in approximately 5% of people at the age of 40, which increases up to 60% in people at the age of 70 or older (5-7). In Western individuals, diverticula are most commonly present in the left colon and particularly in the sigmoid colon (8). Contrarily, in Asian individuals, diverticula are typically present in the right colon and might have a different origin (9).

Although the etiology of diverticulosis is not yet fully understood, it is thought to be multifactorial and involves several factors, such as genetic, lifestyle, and environmental factors (10). Changes in the colonic wall, alterations in gut motility, and increased intracolonic pressure are thought to be the main contributors to the development of diverticula (4, 11). Western dietary habits have been identified to contribute to the development of diverticula. In particular, a low-fiber diet has been associated with diverticulosis, because of its effect on stool transit and intracolonic pressure (11). Consequences of ageing on the colon have been studied and include changes such as collagen cross-linking, elastin depositions, and decreased smooth muscle function (12-14).

Diverticulitis

An estimated 4-7.3% of individuals with diverticulosis will have diverticulitis, which occurs when one or more diverticula get inflamed or infected (15). In the Netherlands, the incidence and prevalence of diverticulosis and diverticulitis are 0.7 and 1.8 per 1000 patients per year and an approximate number of 22,000 patients are referred to secondary care for diverticulitis, annually (16, 17). Recent data from Italy suggest an annual increase of 3% of acute diverticulitis-related hospital admissions between 2008 and 2015, with an increase from 39 to 48 hospitalizations per 100,000 inhabitants (18). Its burden on healthcare is well illustrated by the fact that diverticular disease is the third most common gastrointestinal discharge diagnosis in the United States (19). Moreover, certainly in the light of its increasing incidence, it is an important condition in terms of healthcare costs, which have been estimated to lead up to 2.1 billion U.S. dollars per year (19).

The pathogenesis of diverticulitis is a complex interplay between multiple factors and has not been completely elucidated. At first, it was thought that impaction of diverticula resulted in diverticulitis through increased intradiverticular pressure, with mucosal ulceration, bacterial proliferation, as well as local ischemia and microperforation as a consequence (20, 21). However, in recent years, new evidence has pointed more towards

the role of alterations in gut microbiome composition and function, with subsequent low-grade mucosal inflammation (20).

Several controllable and uncontrollable factors have been identified that put patients at higher risk of the progression of diverticulosis to diverticulitis. Again, it seems that a low-fiber diet plays a role and puts individuals at risk of diverticulitis (22). Moreover, obesity is an important risk factor, whereas physical activity seems to be a protective factor (23). Also, various drugs have been reported to add to the risk of diverticulitis, such as non-steroidal anti-inflammatory drugs, corticosteroids, and opiate analgesics (20, 24).

Acute diverticulitis can either be uncomplicated or complicated. In case of the latter, the inflammatory process leads to complications such as intra-abdominal abscess formation or perforation with purulent or fecal peritonitis. Approximately 10-20% of patients with diverticulitis present with complicated disease (25, 26), which requires more rigorous treatment, because, evidently, it is associated with worse outcomes (e.g. peritonitis, colonic stenosis, fistula) than uncomplicated disease. Hence, it is important to distinguish between these types of acute diverticulitis. Generally, clinical findings alone are not enough to accurately assess disease severity and imaging is required to confirm the diagnosis (27). In the setting of acute diverticulitis, both ultrasound (US) and computed tomography scan (CT) have been investigated and both methods have been demonstrated to have a sensitivity and specificity of over 90% (28, 29). Nevertheless, in case of suspected complicated diverticulitis and in critically ill patients, it is agreed upon that CT is the imaging method of choice (27).

Once complicated diverticulitis is diagnosed, it is further divided into different disease stages for which several classifications have been introduced through the years. Originally, Hinchey *et al.* (30) proposed their classification for acute diverticulitis in 1978, which was based on clinical and surgical findings. However, with the addition of CT imaging in the diagnostic process of acute diverticulitis, several adaptations of the Hinchey classification, as well as novel classifications were introduced (31). Nowadays, one of the most widely used classifications is the modified Hinchey classification as proposed by Wasvary *et al.* (32). This classification describes mild diverticulitis (grade 0), diverticulitis with confined pericolic inflammation or phlegmon (grade Ia), pericolic or mesocolic abscess formation (grade Ib), pelvic, distant intra-abdominal, or retroperitoneal abscess formation (grade II), as well as perforated diverticulitis with purulent (grade III) or fecal (grade IV) peritonitis.

In this thesis, the main focus is put on these different stages of complicated diverticulitis and their non-resectional or resectional management.

Diverticulitis with abscess formation

Of the patients with acute complicated diverticulitis, approximately 15–20% of cases will be complicated by abscess formation (Hinchey Ib and II diverticulitis) (33–35). Over the course of past decades, the treatment of diverticular abscesses has changed significantly. Traditionally, diverticular abscesses were managed surgically. However, facilitated by improvements in disease imaging, interventional radiology and antibiotic treatment, treatment gradually became more conservative (36, 37). Nowadays, non-surgical treatment by means of antibiotics with or without image-guided percutaneous drainage has become standard practice for most cases (36). Importantly, the choice of treatment remains dependent on the patient's clinical presentation, but also on factors affecting the amenability for drainage, such as the location and size of the abscess(es). In efforts to standardize treatment, several guidelines on diverticular disease have stated cut-off values for abscess size on which the choice for percutaneous drainage could partly be based (27). Although mostly based on low-quality evidence, sizes ranging from 3–5 centimeters or larger were used to define large abscesses that require drainage in addition to antibiotic treatment (38, 39). In addition to initial treatment outcomes, it is also important to consider the rate of long-term adverse outcomes, such as recurrent diverticular disease, surgery, or recurrence-related mortality. Recurrence and long-term surgery rates have been reported to be as high as 25% and 18.2%, respectively, although most studies were small, observational and of retrospective design (40). Hence, this emphasizes the need for strong evidence to support accurate patient selection and to help guide adequate treatment choices.

Perforated diverticulitis with purulent or fecal peritonitis

The first scientific report on the surgical treatment of diverticulitis dates back to 1907 (41). Ever since, the optimal surgical management of perforated diverticulitis has been a frequently debated topic and, consequently, standards have changed several times. Whereas at first a three-stage procedure was advocated, during the course of the second half of the 20th century, a two-staged approach became increasingly popular (42). This approach was named after the French surgeon Henri Hartmann, who already introduced it in 1923, although not for complicated diverticulitis but for rectum carcinoma (43). It involves resection of the diseased segment, construction of a colostomy, closure of the rectal stump, and – during a second procedure – restoration of intestinal continuity (42). Later on, during the past three decades, this ‘gold standard’ for perforated diverticulitis became challenged by novel one-stage approaches, such as laparoscopic peritoneal lavage and sigmoidectomy with primary anastomosis.

Results of the non-resectional treatment of perforated diverticulitis with purulent peritonitis by means of laparoscopic peritoneal lavage were first published in 1996 (44). As the laparoscopic lavage procedure was considered less invasive and avoided the need for stoma construction, it gained increased interest soon after early results seemed positive (45). Lavage was deemed suitable for Hinchey III diverticulitis of which the idea is that it results from a perforated abscess while the original diverticular perforation is sealed off. Obviously, lavage was not deemed suitable in those cases in which an overt connection between the bowel and abdominal cavity is present (Hinchey IV) or in cases of peritonitis caused by misdiagnosed perforated cancer. Subsequently,

randomized controlled trials comparing laparoscopic lavage to sigmoid resection in Hinchey III patients were initiated and conducted (46-48). Conclusions based on the results of these trials differed and, interestingly, conclusions of the several meta-analyses that synthesized evidence from these trials were also conflictive. In general, a higher short-term failure risk after lavage needs to be weighed against the benefits such as a lower percentage of stomas and secondary procedures (e.g. stoma reversal) during the later stages of follow-up. Recently, research has focused more on long-term outcomes, as well as on the identification of risk factors for treatment failure to aid the identification of patients who might benefit most from laparoscopic lavage and who are at low risk for short-term failure.

With regard to sigmoidectomy with primary anastomosis, an important aspect to withhold surgeons from performing this one-stage procedure was the fear of anastomotic leakage in the setting of peritonitis. Nevertheless, some factors, such as the improvement in the management of sepsis, have helped gain increased interest for this approach. Despite its inherent risk of anastomotic leakage, the procedure was thought to have some significant advantages over the Hartmann's procedure. In the vast majority of cases, a defunctioning ileostomy is constructed during the primary anastomosis procedure. In contrast to the Hartmann's reversal, ileostomy reversal is technically less challenging with a lower risk of leakage and, therefore, was hypothesized to lead to higher stoma reversal rates and less complications after the reversal procedure. Several pro- and retrospective observational cohort studies were published that confirmed these advantages. These studies demonstrated that patients undergoing primary anastomosis had similar or less morbidity and mortality as compared to the Hartmann's procedure, as well as higher stoma reversal rates with less reversal-related morbidity (35, 49-51). However, importantly, most of these studies were at risk for confounding by indication, leading (relatively) healthier patients to be selected to undergo sigmoidectomy with primary anastomosis. To overcome this risk of bias, randomized controlled trials were initiated with the goal to compare both procedures for Hinchey III and IV diverticulitis.

Stoma-related complications

As mentioned before, in the vast majority of patients undergoing emergency surgery for perforated diverticulitis a stoma is constructed. However, a number of other indications exists for which the construction of a definite or temporary stoma is required, such as surgery for colorectal cancer, inflammatory bowel disease, or urological indications. Next to having a significant impact on factors such as body image and social functioning (52), the presence of a stoma also puts patients at risk for the development of a parastomal hernia.

Often defined as an incisional hernia related to an abdominal wall stoma, parastomal hernia is a common complication and incidence rates depend on the type of stoma, diagnostic methods, as well as the length of follow-up (53). In case of end colostomies, incidence rates range from 4.0 to 48.1%, whereas rates for loop ileostomies range from 0.0 to 6.2% (54). Parastomal hernias can lead to several problems, such as pain, problems with stoma appliance handling, leakage, bowel obstruction, and incarceration (53). There are several surgical options for the management of parastomal hernia (55). However, it remains

debated if in some patients ‘watchful waiting’ might also be appropriate, an approach that is also seen in incisional and inguinal hernia management (56, 57).

Importantly, the incision site of the stoma also remains vulnerable for herniation after patients undergo stoma reversal, which puts these patients at risk for the development of a stoma site incisional hernia. Similar to a parastomal hernia, a stoma site incisional hernia can lead to pain, discomfort, and incarceration. In recent years, the incidence, risk factors, and potential methods for prevention have gained increased attention, which will also be touched upon in this thesis.

Postoperative ileus

As opposed to the more long-term problem of abdominal wall hernia after surgery, postoperative ileus is a problem that arises shortly after the procedure. Postoperative ileus is generally defined as prolonged inhibition of gastrointestinal motility after surgery, although there is a wide variety in reported definitions throughout the literature (58, 59). Due to the different definitions reported, the true incidence of (prolonged) postoperative ileus is difficult to estimate, but seems to range between 10 to 30% of patients undergoing abdominal surgery (60, 61). Symptoms might include nausea, vomiting, intolerance of oral intake, abdominal distension, and lack of defecation, which results in lengthened hospital stay, a higher risk of hospital-acquired infections, as well as an increase in costs (59, 62).

The pathophysiology of postoperative ileus is complex and involves both neurogenic and inflammatory factors that are triggered by surgery and its inherent gut manipulation (63). Next to the development of enhanced recovery protocols, numerous other strategies for the prevention and treatment of postoperative ileus have been assessed, such as chewing gum, prokinetic agents (e.g. magnesium oxide, metoclopramide), and peripheral μ -opioid receptor antagonists (e.g. Alvimopan) (59). In recent years, the role of the vagus nerve and cholinergic anti-inflammatory pathway have been investigated as potential mechanism to help prevent postoperative ileus, for example, by means of vagus nerve stimulation (63). Hence, it was hypothesized that nicotine chewing gum might be an inexpensive and widely available option to prevent postoperative ileus, both by activation of the cephalic-vagal reflex through chewing, as well as by activation of the cholinergic anti-inflammatory pathway due to nicotine administration (64).

Aims and outline of this thesis

The aim of this thesis is to investigate and help improve the management of complicated diverticulitis by focusing on both its non-resectional, as well as its resectional treatment. Moreover, stoma-related complications and the prevention of postoperative ileus will be addressed.

Part I of this thesis focuses on the non-resectional treatment of complicated diverticulitis.

Chapter 2 describes a retrospective, multicenter cohort study of patients with Hinchey Ib and II diverticulitis, in which short- and long-term outcomes of non-surgical treatment by means of antibiotics with or without percutaneous drainage are assessed.

Chapter 3 is a follow-up study of a cohort of patients who underwent laparoscopic peritoneal lavage for perforated diverticulitis, which describes long-term outcomes, such as recurrent diverticulitis, reoperations, and readmissions.

In **Chapter 4**, the role of laparoscopic lavage for the treatment of perforated diverticulitis is further discussed, providing a comprehensive overview of the currently available evidence.

In **Part II** strategies for the resectional treatment of complicated diverticulitis are addressed.

Chapter 5 describes the clinical and patient-reported outcomes of the DIVA arm of the international, multicenter, randomized Ladies trial, comparing Hartmann's procedure to sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or fecal peritonitis.

In **Chapter 6**, the cost-effectiveness analysis of this study is described.

Chapter 7 is a systematic review and meta-analysis of observational and experimental studies comparing both these surgical procedures for the same indication of perforated diverticulitis with peritonitis.

In **Part III** the existing evidence on the treatment of diverticulitis is appraised.

Chapter 8 is a narrative review and addresses several important topics in the multidisciplinary management of complicated diverticulitis.

In **Chapter 9** all the available evidence on a broad range of topics, including the epidemiology, classification, diagnostics, and management of both uncomplicated and complicated diverticulitis, is appraised and presented as a result of the efforts of the European Society of Coloproctology guideline committee.

Part IV focuses on stoma-related complications.

Chapter 10 describes a multicenter, retrospective cohort study in which a comparison is made between a non-operative ('watchful waiting') strategy and surgical treatment, in terms of choice of treatment reasons, cross-over rates, and complications.

Chapter 11 describes a systematic review assessing the comparability of the different diagnostic modalities reported throughout the literature, as there is a large variance in reported rates of parastomal hernia.

Chapter 12 is a systematic review and meta-analysis with the aim to assess the incidence, risk factors and prevention of stoma site incisional hernia.

In **Part V** focus is put on the prevention of postoperative ileus.

Chapter 13 describes a double-blind, randomized pilot study in which the effects of nicotine chewing gum are compared to regular chewing gum in terms of their effect on gastrointestinal motility after elective oncological colorectal surgery.

In **Chapter 14** results from all chapters will be discussed and future perspectives will be described. Lastly, **Chapter 15** and **Chapter 16** summarize the results presented in this thesis in English and Dutch.

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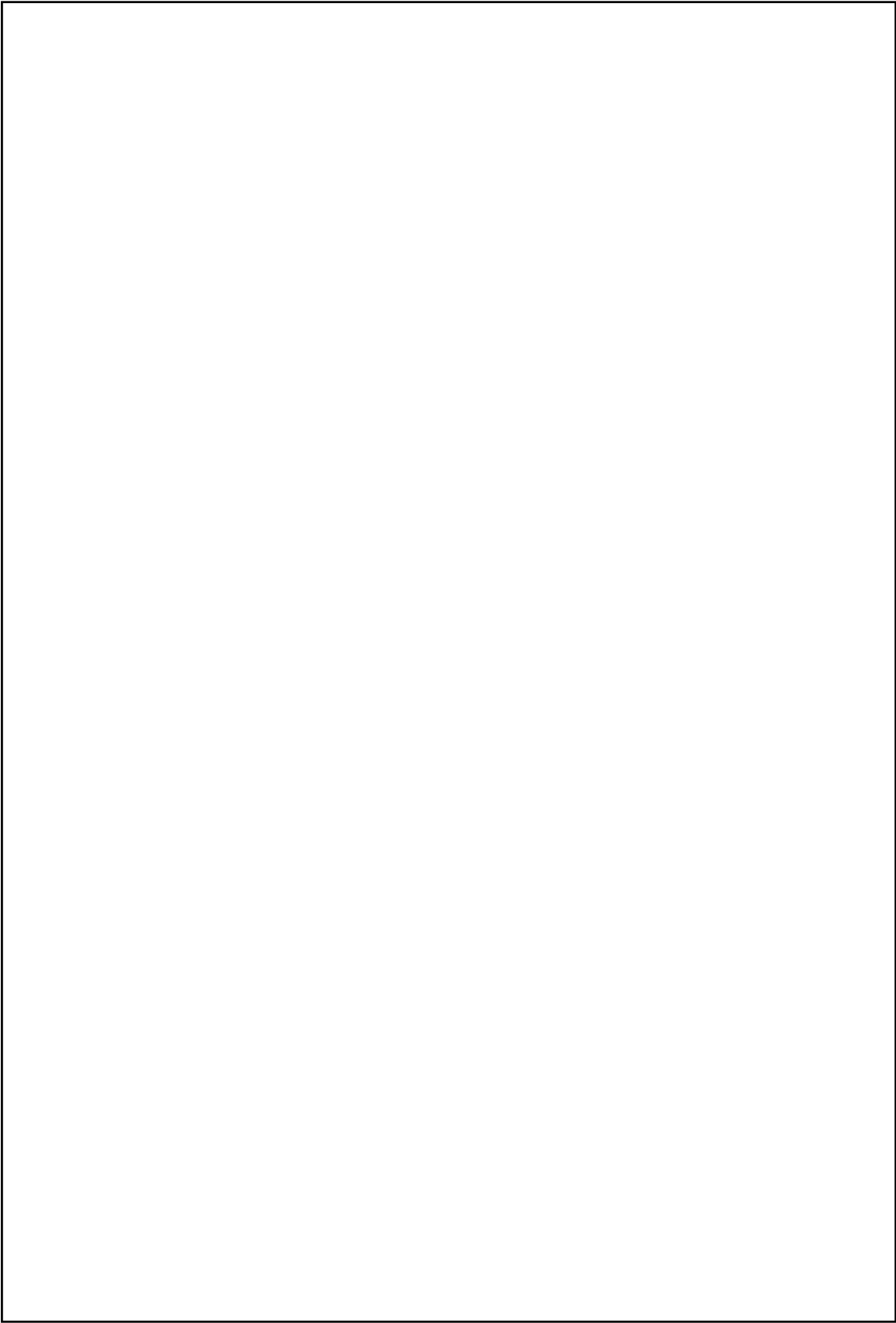
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Part I

Non-resectional treatment of complicated diverticulitis



Chapter 2

Multicentre study of non-surgical management of diverticulitis with abscess formation

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British Journal of Surgery 106.4 (2019): 458-466.

Abstract

Background

Treatment strategies for diverticulitis with abscess formation have shifted from (emergency) surgical treatment to non-surgical management (antibiotics with or without percutaneous drainage (PCD)). The aim was to assess outcomes of non-surgical treatment and to identify risk factors for adverse outcomes.

Methods

Patients with a first episode of CT-diagnosed diverticular abscess (modified Hinchey Ib or II) between January 2008 and January 2015 were included retrospectively, if initially treated non-surgically. Baseline characteristics, short-term (within 30 days) and long-term treatment outcomes were recorded. Treatment failure was a composite outcome of complications (perforation, colonic obstruction and fistula formation), readmissions, persistent diverticulitis, emergency surgery, death, or need for PCD in the no-PCD group. Regression analyses were used to analyse risk factors for treatment failure, recurrences and surgery.

Results

Overall, 447 patients from ten hospitals were included (Hinchey Ib 215; Hinchey II 232), with a median follow-up of 72 (i.q.r. 55–93) months. Most patients were treated without PCD (332 of 447, 74.3 per cent). Univariable analyses, stratified by Hinchey grade, showed no differences between no PCD and PCD in short-term treatment failure (Hinchey I: 22.3 *versus* 33 per cent, $P = 0.359$; Hinchey II: 25.9 *versus* 36 per cent, $P = 0.149$) or emergency surgery (Hinchey I: 5.1 *versus* 6 per cent, $P = 0.693$; Hinchey II: 10.4 *versus* 15 per cent, $P = 0.117$), but significantly more complications were found in patients with Hinchey II disease undergoing PCD (12 *versus* 3.7 per cent; $P = 0.032$). Multivariable analyses showed that treatment strategy (PCD *versus* no PCD) was not independently associated with short-term treatment failure (odds ratio (OR) 1.47, 95 per cent c.i. 0.81 to 2.68), emergency surgery (OR 1.29, 0.56 to 2.99) or long-term surgery (hazard ratio 1.08, 95 per cent c.i. 0.69 to 1.69). Abscesses of at least 3 cm in diameter were associated with short-term treatment failure (OR 2.05, 1.09 to 3.86), and abscesses of 5 cm or larger with the need for surgery during short-term follow-up (OR 2.96, 1.03 to 8.13).

Conclusion

The choice between PCD with antibiotics or antibiotics alone as initial non-surgical treatment of Hinchey Ib and II diverticulitis does not seem to influence outcomes.

Introduction

Diverticulosis is common in the Western world and is estimated to affect more than half of the population over the age of 65 years(1). Diverticulosis might lead to diverticulitis in approximately 4.3-7% of cases(2, 3), of which 25 per cent present with acute complicated diverticulitis; this can consist of severe complications, such as abscess, perforation, stenosis or fistula(4). Abscess formation occurs in approximately 15 per cent of patients with acute complicated diverticulitis(5-7). It can be classified according to the modified Hinchey classification as type Ib (confined pericolic abscess smaller than 5 cm) or Hinchey II (pelvic, distant intra-abdominal or retroperitoneal abscess at least 5 cm in size)(8, 9).

Over the years, treatment strategies for diverticulitis with abscess formation have gradually shifted from (emergency) surgical treatment to non-surgical management comprising antibiotics with or without percutaneous drainage (PCD)(10). Currently, guidelines(11-13) advise that small pericolic abscesses can be treated with antibiotics, whereas distant (pelvic) or larger abscesses, usually defined as those with a diameter of 3-5 cm or larger, should be treated with PCD, if possible. As patients undergoing non-surgical treatment are at risk of adverse outcomes such as emergency surgery, disease recurrence, readmission and even death (both in the short and long term)(10, 14), adequate patient selection for the optimal choice of treatment has come to play an important role in the management of these patients.

However, the clinical course of complicated diverticulitis with abscess formation after non-surgical treatment, as well as the risk factors for adverse outcomes, have not been analysed adequately(10, 12). Most of the existing studies(15-22) addressing these topics are limited by a short follow-up, small and single institutional study populations and a lack of time-to-event analysis.

Therefore, the primary aim of this multicentre retrospective study was to assess both the short- and long-term outcomes of initial non-surgical treatment strategies for acute complicated diverticulitis with abscess formation (Hinchey Ib and II) in a large number of patients. The second aim was to identify risk factors associated with adverse outcomes, to help facilitate adequate patient selection and assess the optimal treatment strategy.

Methods

This multicentre retrospective study was conducted in two academic and eight teaching hospitals in the Netherlands. The study was approved by the institutional review boards of all participating hospitals. This article was written in accordance with the STROBE statement and checklist(23). All patients aged 18 years and older, who had a first episode of CT-diagnosed complicated diverticulitis with abscess formation (modified Hinchey Ib or II(8)), and who had initial non-surgical treatment, being either antibiotic treatment (no PCD) or antibiotic treatment with PCD, were eligible for inclusion in the cohort. Patients with perforated diverticulitis with peritonitis (Hinchey III or IV) and those with signs of sepsis or concurrent fistula formation were excluded. Potentially eligible patients who presented between 1 January 2008 and 31 January 2015 were sought by using a diagnosis-specific code (Diagnose Behandelend Combinatie or Diagnosis Related Group), ICD-9 or ICD-10 codes in all hospital databases. In Gelre Hospital, patients could only be identified between 1 January 2012 and 31 January 2015. Subsequently, patients' medical records were screened for inclusion and exclusion criteria before definitive inclusion in the study cohort.

Data collection

All medical records were reviewed retrospectively. Baseline patient characteristics were collected, such as age, BMI, co-morbidities, medical and surgical history, previous episodes of uncomplicated diverticulitis, medication, smoking, alcohol consumption and ASA fitness grades. Radiological details of the number, location and size of abscesses were recorded, as well as clinical signs and symptoms (nausea, vomiting, bowel complaints, rectal blood loss), and laboratory parameters (C-reactive protein (CRP) and white blood cell count (WBC)). The largest reported size of the abscess was used as the measure of abscess size. Details of treatment were recorded, including type and duration of antibiotic treatment, PCD (approach, type of drain and duration of drainage) and surgical procedures (for example, elective or emergency resection or stoma reversal surgery).

Outcomes

Short-term outcomes were: treatment failure, complications (colonic obstruction, perforation and fistula formation), clinical deterioration/progression of disease, emergency surgery (all unscheduled operations), readmissions, persistent diverticulitis (complaints lasting more than 30 days) and death. Long-term outcomes were: recurrent (un)complicated diverticulitis episodes, sigmoid resection and death. Short term was defined as the first 30 days after diagnosis of abscess, or during the primary admission if a patient was still in hospital after 30 days, whereas long term was defined as the period thereafter. Treatment failure was defined as the composite outcome of complications, readmissions, persistent diverticulitis, emergency surgery, death or need for PCD in the no-PCD group. Recurrent diverticulitis was registered as complicated in the presence of a phlegmon, abscess, fistula, stenosis or perforation, whereas uncomplicated diverticulitis was registered if it was mentioned in the medical record as recurrent disease, in the absence of the abovementioned complications.

Statistical analysis

Multiple imputation techniques were used to impute missing data to avoid selection bias. Data were assumed to be missing at random. All reported results are based on the imputed data, where the estimates of interests at the final computational step were combined across the imputed data sets using Rubin's rules(24). Continuous variables are presented as mean (s.d.) or median (i.q.r.), depending on the normality of data distribution, and compared using the independent t test or Mann–Whitney U test, as appropriate. Categorical variables are presented as numbers with percentages, and were analysed using Pearson's χ^2 test and Fisher's exact test. Differences in patient and disease characteristics between patients with and without treatment failure and emergency surgery were assessed to identify risk factors for these outcomes. Univariable logistic regression analyses were used to calculate crude odds ratios (ORs) with 95 per cent confidence intervals. Inclusion of relevant diagnostic items in the multivariable model, to identify independent predictors, was based on clinical knowledge and P values ($P < 0.200$ or $P < 0.050$, depending on the event rate). Recurrence and sigmoid resection in the long term were assessed by means of Kaplan–Meier estimates, stratified by Hinchey classification and treatment (no PCD *versus* PCD), with censoring at the end of study follow-up or death. The effect of Hinchey classification and treatment on the outcome was assessed by means of the Mantel–Cox log rank test. Cox proportional hazards regression was used to analyse risk factors for recurrence and sigmoid resection in the long term. Hazard ratios (HRs) with 95 per cent confidence intervals are presented for co-variables associated with recurrence or sigmoid resection during long-term follow-up. Differences between hospitals could have an effect on treatment outcomes; to test for this bias by clustering of data, the short and long-term analyses were also adjusted for hospital. Short-term outcomes were adjusted by fitting a generalized linear mixed model for each outcome, using a logistic regression mixed model. Hinchey classification and PCD were entered separately as fixed effects and hospital as a random effect. For the short-term multivariable logistic regression analyses, hospital was entered as a co-variable in each multivariable model. Long-term Cox regression analyses were adjusted by entering hospital as a co-variable in each multivariable model. Finally, sensitivity analyses of the non-imputed data set were undertaken to test whether the imputation technique had any influence on the outcomes of interest. All analyses were done using SPSS® version 24.0 (IBM, Armonk, New York, USA).

Results

Patient and disease characteristics are shown in *Table 1*. A total of 447 patients with CT-proven Hinchey type Ib (215 patients) or II (232) diverticulitis were included. The Academic Medical Centre contributed 20 patients (4.5 per cent), Erasmus University Medical Centre 11 (2.5 per cent), Meander Medical Centre 69 (15.4 per cent), Havenziekenhuis 4 (0.9 per cent), IJsselland Hospital 24 (5.4 per cent), Amphia Hospital 84 (18.8 per cent), Reinier de Graaf Gasthuis 32 (7.2 per cent), Onze Lieve Vrouwe Gasthuis 99 (22.1 per cent), Gelre Hospital 51 (11.4 per cent) and Catharina Hospital 53 (11.9 per cent). The mean(s.d.) age of the patients was 61(13) years and 40.7 per cent were men. The mean BMI of the total cohort was 27.8(5.7) kg/m². Some 271 patients (60.6 per cent) had co-morbidities and 123 (27.5 per cent) had an ASA fitness grade above II. The mean CRP level was 168(106) mg/l for the total cohort and mean WBC was 14.8(5.2) $\times 10^9$ /l.

Most patients were treated with amoxicillin–clavulanic acid (90 of 289, 31.1 per cent), cefuroxime and metronidazole (88 of 289, 30.4 per cent), ceftriaxone and metronidazole (41 of 289, 14.2 per cent), or other antibiotics (70 of 289, 24.2 per cent) such as clindamycin, co-trimoxazole or piperacillin tazobactam; median duration of antibiotic treatment was 7 (i.q.r. 5–12) days. Information on route of antibiotic administration was available for 174 of 332 patients in the no-PCD group and 67 of 115 in the PCD group; 36 (20.6 per cent) and six (9 per cent) patients respectively received oral antibiotics. Most patients (332, 74.3 per cent) were initially treated without PCD; the remaining 115 patients (26.7 per cent) underwent PCD for a median of 6 (3–16) days. The PCD approach was mainly transabdominal (86 of 115, 74.8 per cent), guided by either ultrasound imaging (49 of 115, 42.6 per cent) or CT (63 of 115, 54.8 per cent). Median duration of hospital stay was 7 (5–13) days and median follow-up was 72 (55–93) months.

Levels of inflammatory parameters were higher in the PCD group, with a mean CRP concentration of 222(114) mg/l compared with 149(96) mg/l in the no-PCD group, and mean WBC of 16.3(5.6) *versus* 14.3(4.9) $\times 10^9$ /l respectively. A larger proportion of patients in the PCD group were classified as having Hinchey II disease (84.3 *versus* 40.7 per cent), and with multiple abscesses (20.0 *versus* 12.0 per cent). Of 63 patients with multiple abscesses, four were known to use corticosteroids, one to use mycophenolic acid, and one patient had undergone renal transplantation, whereas none of these patients received chemotherapy around the time of presentation. Median abscess diameter was 6.4 (5.0–8.5) cm in the PCD group compared with 3.6 (2.5–5.1) cm in the group treated without PCD. Median duration of hospital stay was longer in the PCD group: 10 (7–18) *versus* 7 (4–10) days.

Missing data

All candidate predictors had missing data, except age, sex and ASA classification. Most variables had between 1 and 20 per cent missing data. Three variables had a large amount of missing data: BMI (47.9 per cent), smoking (60.6 per cent) and alcohol consumption

(64.2 per cent). For abscess size, 31.5 per cent of data were missing. In total, 2140 data items (14.9 per cent) were imputed.

Short- and long-term outcomes

Short- and long-term outcomes are summarized in *Table 2*. Of the total cohort, 120 patients (26.8 per cent) experienced treatment failure and 40 (8.9 per cent) required emergency surgery within 30 days after first presentation. One patient had operative drainage and a stoma was constructed in three patients, two of whom also underwent sigmoid resection in a second stage. Seventy-one patients (15.9 per cent) were readmitted to hospital within 30 days after first presentation and 63 (14.1 per cent) had persistent diverticulitis. Overall, 16 patients in the no-PCD group (4.8 per cent) underwent PCD during short-term follow-up and two in the PCD group (1.7 per cent) had a second PCD procedure. Five patients (1.1 per cent) died from severe sepsis caused by perforated diverticulitis. Three of these patients died after undergoing emergency surgery, whereas two did not have surgery or receive further treatment owing to co-morbidity. In all, 122 patients (27.3 per cent) experienced one or more episodes of recurrent diverticulitis. In total, 166 episodes of recurrent diverticulitis were recorded, of which 94 (56.6 per cent) were uncomplicated and 72 (43.4 per cent) were complicated. Median time to recurrence was 8 (3–24) months. Eighteen patients (14.8 per cent) had a first recurrence within 1 month after the end of short-term follow-up.

During long-term follow-up, 13 patients (2.9 per cent) underwent PCD, seven in the no-PCD and six in the PCD group. A total of 124 patients (27.7 per cent) required sigmoid resection, 14 in an emergency setting. Median time to operation was 5 (3–13) months. Twenty-eight patients died (6.3 per cent) during long-term follow-up, two from diverticulitis-related causes. One of these patients died from severe sepsis caused by anastomotic leakage after Hartmann reversal surgery, and one from severe sepsis owing to intestinal ischaemia after sigmoid resection for diverticular stenosis. Overall, data on colonic evaluation was available for 394 patients, of whom 239 (PCD 58, no PCD 181) underwent colonoscopy during follow-up after a median of 10.9 (7.0–21.6) weeks. A malignancy was found in 12 of these patients, including nine in the no-PCD group ($P = 1.000$).

During short-term follow-up, patients in the PCD group had significantly more emergency resections (13.9 *versus* 7.2 per cent; $P = 0.030$), as well as complications, treatment failure and clinical deterioration/disease progression. In analyses stratified by Hinchey grade, among patients with Hinchey II disease, significantly more complications were found in the PCD group (12 *versus* 3.7 per cent; $P = 0.032$). *Figs 1* and *2* show the time-to-event analyses of recurrence and surgery during long-term follow-up; there were no significant differences in recurrence ($P = 0.544$) or surgery ($P = 0.088$). Overall, patients in the PCD group had significantly more complications during long-term follow-up (24.3 *versus* 13.9 per cent; $P = 0.009$), which was also evident in the Hinchey Ib subgroup (39 *versus* 12.7 per cent; $P = 0.016$). The mortality rate was higher in the PCD group (10.4 *versus* 4.8 per cent; $P = 0.048$). In the subgroup with Hinchey II disease, there were more sigmoid resections among patients who underwent PCD (32

versus 22.2 per cent; $P = 0.046$). No other differences between treatment groups were found in short- and long-term outcomes.

Risk factors for treatment failure and emergency surgery during short-term follow-up

Univariable analyses of all possible predictors for treatment failure and emergency surgery are shown in *Table S1* (supporting information). Different cut-off sizes for abscess diameter were reviewed univariably to analyse which could best predict outcome. A cut-off size of 3 cm seemed to be the best predictor of treatment failure (univariable OR 2.33, 95 per cent c.i. 1.32 to 4.11), and a cut-off size of 5 cm the best predictor of emergency surgery (univariable OR 2.97, 1.28 to 6.85). The results of multivariable analysis are shown in *Table 3*. A higher BMI slightly decreased the risk of treatment failure (OR 0.94, 0.89 to 0.997), whereas an abscess size of at least 3 cm increased the risk (OR 2.05, 1.09 to 3.86). With regard to emergency surgery, history of abdominal surgery increased the risk (OR 2.05, 1.04 to 4.05), as did an abscess size of 5 cm or larger (OR 2.96, 1.08 to 8.13). No other variable had an effect on the risk of treatment failure or emergency surgery. Two separate subgroup analyses were performed to assess the effect of PCD on the outcome for different abscess sizes (at least 3 cm and at least 5 cm). The first included only the 324 patients with an abscess of 3 cm or larger. In this subgroup, there were no differences in rate of treatment failure between patients treated with (109) or without (215) PCD (35.7 versus 28.4 per cent respectively; $P = 0.200$), or in rate of emergency surgery (14.3 versus 9.3 per cent; $P = 0.198$). The second subgroup analysis included only the 185 patients with an abscess size of at least 5 cm. In this subgroup, there were also no differences in rate of treatment failure between patients treated with (94) and without (91) PCD (35 versus 28 per cent respectively; $P = 0.409$), or in rate of emergency surgery (16 versus 12 per cent; $P = 0.416$).

Risk factors for recurrence and sigmoid resection during long-term follow-up

Univariable analyses of all possible predictors for treatment failure and emergency surgery during long-term follow-up are shown in *Table S2* (supporting information) and results of the subsequent multivariable analysis in *Table 4*. A history of diverticulitis increased the risk of recurrence (HR 1.71, 95 per cent c.i. 1.17 to 2.48). A history of abdominal surgery (HR 0.63, 0.42 to 0.98) and sigmoid resection (HR 0.15, 0.05 to 0.48) decreased the risk of recurrence. Older patients seemed to be at slightly higher risk of sigmoid resection during long-term follow-up (HR 1.02, 1.001 to 1.03) and the symptoms vomiting (HR 1.82, 1.13 to 2.93) and nausea (HR 1.72, 1.03 to 2.85) also increased this risk. No other variable had an effect on the occurrence of sigmoid resection during long-term follow-up.

Sensitivity analyses

Overall, sensitivity analyses of the non-imputed data set showed similar results for short- and long-term outcomes, and short-term complications and emergency resection were not significantly different in hospital-adjusted analyses (*Table S3*, supporting information). Stratified analyses by Hinchey grade showed significant differences in the non-imputed data for short-term readmission and persistent diverticulitis (*Table S4*, supporting information). In addition, sensitivity analyses of the non-imputed data set

and hospital-adjusted analyses were undertaken for multivariable logistic regression and Cox regression analyses (*Tables S5 and S6*, supporting information).

Discussion

In the present study, multivariable analysis showed that initial non-surgical treatment of Hinchey Ib and II diverticular abscesses (antibiotics alone *versus* PCD in combination with antibiotics) had no independent effect on short- and long-term outcomes. Abscess size of at least 3 cm was identified as an independent risk factor for short-term treatment failure, and 5 cm or more as an independent risk factor for short-term emergency surgery. Previous studies of treatment outcomes of diverticular abscesses have been limited by factors such as small and single-institution study populations, a lack of time-to-event analysis and short follow-up(10, 12). The cohort study of 3148 patients with Hinchey stage Ib and II disease investigated by Gregersen and colleagues(25, 26) remains the largest reporting on both short- and long-term treatment outcomes. However, an important limitation of that study was the absence of data on the clinical condition of the patients, as well as data on abscess size and location. This complicates comparison of treatment modalities because, owing to the introduction of selection bias and confounding, differences in outcomes may primarily reflect disease and clinical severity. The present study, with a total of 447 patients, took these patient and disease characteristics into account, and also assessed long-term outcomes. The comparison of PCD and no PCD in this cohort showed that patients who underwent PCD seemed to have worse outcomes, in terms of a greater likelihood of short-term emergency resections, complications, disease progression and treatment failure, as well as more long-term complications. However, confounding by indication cannot be excluded from this analysis and differences may primarily reflect disease and clinical severity. Indeed, patients undergoing PCD had more advanced disease than those in the no-PCD group, with the majority of patients having Hinchey stage II disease (84.3 *versus* 40.7 per cent; $P < 0.001$). Patients in the PCD group had larger abscesses, as well as significantly more distant abscesses or multiple abscesses. Hence, when the patients were stratified by Hinchey grade, most short- and long-term outcomes did not differ between the PCD and no-PCD groups, with the exception of short-term complications and long-term resections among patients with Hinchey II disease, and long-term complications in those with Hinchey Ib diverticulitis. More importantly, in the multivariable analyses, the initial treatment strategy did not seem to be a predictor with regard to treatment failure, emergency surgery, or sigmoid resection in long-term follow-up, strengthening the conclusion that treatment strategy has no effect on the outcome.

The short-term mortality rate in the present study ranged between 0 and 2 per cent across the groups analysed, which is comparable to pooled average mortality rates derived from previous studies of treatment with antibiotics (0.6 per cent) and PCD (1.6 per cent)(14). Short-term emergency surgery rates ranged from 5.1 to 15 per cent, which is also largely in accordance with the pooled average of 12.1 per cent (14). Reported rates of diverticulitis recurrence vary from 3 to 68 per cent, with an average of 28 per cent; recurrent disease consists mostly of uncomplicated or locally complicated

diverticulitis(10). Although rates may vary between studies because of differences in median follow-up or in definitions, the recurrence rates reported in the present study seem to be in line with earlier reports (27, 28). In light of the long-term surgery and recurrence rates in the present study, which were relatively low (and the recurrences mostly uncomplicated), it can be questioned whether elective surgery is indicated in conservatively managed patients, as surgery comes with an inherent risk of complication and most patients seem to fare well with conservative management alone.

The rates of adverse and unwanted outcomes in patients with diverticular abscess remain high and present a major burden to the patient, as well the healthcare system. Therefore, an aim of the present study was to identify potential risk factors related to these adverse outcomes in order to help improve individual patient management. Abscess size was shown to be an independent predictor of adverse outcome; an abscess diameter of at least 3 cm increased the risk of short-term treatment failure, whereas an abscess of 5 cm or larger increased the risk of emergency surgery. These results indicate that, for abscesses larger than 3 cm, and particularly those larger than 5 cm, it can still be debated which treatment strategy is most appropriate, as the results show no definite advantage of one strategy over the other in short-term outcomes. Treatment should not be based solely on abscess size, but other patient and disease characteristics should also be considered. However, no other significant predictors were found in the multivariable analyses for treatment failure or emergency surgery, making it difficult to select a subpopulation of patients who would benefit from PCD. The findings do seem to acknowledge that a cut-off value of 3 cm is appropriate for differentiating between small and large abscesses (11, 13, 17, 29, 30).

An important limitation of this study is its retrospective design, which introduces the potential for selection bias and confounding by indication. However, registration of a wide range of baseline patient and disease characteristics allowed correction for potential known confounders in multivariable logistic and Cox regression analyses. Another inevitable consequence of retrospective observational research is the potential risk of missing data, as the availability of baseline and outcome data is largely dependent on the completeness of medical records. It was hypothesized that re-evaluation of CT images by one or more radiologists could have led to the introduction of (hindsight) bias, as a result of the radiologists' foreknowledge of the reasons for and outcomes of reviewing the images. To prevent selection bias introduced by missing data, multiple imputation methods were used to handle the missing data. Sensitivity analyses of the non-imputed data set did not significantly change the results. With regard to outcome data, it is possible that patients might have received care at a general practitioner or in other hospitals during follow-up, creating the potential for an underestimation of disease recurrences and readmissions. Finally, the multicentre setting of this study could have introduced heterogeneity through between-hospital differences in treatment, such as reasons for choosing PCD or criteria for drain removal. However, these differences were considered small, because all hospitals base their practice on the national guideline for treatment of acute diverticulitis and hospital-adjusted analyses showed comparable outcomes. In addition, the multicentre setting had beneficial effects by increasing both the study's generalizability and sample size. This study of a large cohort of patients with

Hinchey stage Ib and II abscesses has provided evidence that patients with abscesses of at least 3 or 5 cm are at a higher risk of short-term treatment failure or emergency surgery respectively, regardless of the choice of non-surgical treatment strategy. As no clear difference between the two treatment strategies was found, it remains debatable how to treat these patients appropriately. Nevertheless, these data help facilitate informed and shared decision-making, as well as providing valuable information for future prospective studies regarding PCD treatment in patients with abscess formation.

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Tables

Table 1 Baseline characteristics

	Total cohort (n = 447)	No PCD (n = 332)	PCD (n = 115)	P[§]
Patient demographics				
Age (years)*	61(13)	60(13)	63(13)	0.140 [§]
Sex ratio (M : F)	182 : 265	139 : 193	43 : 72	0.400
BMI (kg/m ²)*	27.8(5.7)	27.6(5.5)	28.4(6.3)	0.404 [§]
Smoking	227 (51.0)	167 (50.3)	61 (53.0)	0.603
Alcohol consumption	232 (51.9)	178 (53.6)	54 (47.0)	0.274
Co-morbidities				
ASA fitness grade >II	123 (27.5)	84 (25.3)	39 (33.9)	0.075
Patients with registered co-morbidity	270 (60.6)	201 (60.5)	70 (60.9)	0.952
Medical history				
History of diverticulitis	137 (30.6)	93 (28.0)	44 (38.3)	0.035
History of abdominal surgery	151 (33.8)	119 (35.8)	32 (27.8)	0.130
Medication				
NSAIDs	182 (40.7)	133 (40.1)	49 (42.6)	0.573
Steroids	43 (9.4)	35 (10.5)	8 (7.0)	0.239
Clinical symptoms				
Duration of symptoms (days)†	7 (3–14)	7 (3–12)	8 (4–14)	0.062 [#]
Nausea	236 (52.8)	163 (49.1)	73 (63.5)	0.018
Vomiting	108 (24.2)	65 (19.6)	43 (37.4)	0.001
Diffuse abdominal pain	61 (13.6)	44 (13.3)	16 (13.9)	0.704 ^{**}
Change in bowel habit	294 (65.8)	221 (66.6)	73 (63.5)	0.548
Rectal blood loss	70 (15.7)	44 (13.3)	26 (22.6)	0.044
Clinical signs				
Rebound tenderness	141 (31.5)	104 (31.3)	37 (32.1)	0.602
Local muscular guarding/resistance	115 (25.7)	81 (24.4)	34 (29.6)	0.259
Diffuse muscular guarding	50 (11.2)	32 (9.6)	18 (15.7)	0.255 ^{**}
Temperature (°C)*	37.7(0.9)	37.7(0.9)	37.8(1.0)	0.319 [§]
Laboratory parameters*				
C-reactive protein (mg/l)	168(106)	149(96)	222(114)	< 0.001 [§]
White blood cell count (× 10 ⁹ /l)	14.8(5.2)	14.3(4.9)	16.3(5.6)	0.001 [§]
Radiological parameters				
Hinchey II‡	232 (51.9)	135 (40.7)	97 (84.3)	< 0.001
Largest abscess diameter (cm)†	4.2 (2.7–6.1)	3.6 (2.5–5.1)	6.4 (5.0–8.5)	< 0.001 [#]
Distant location of abscess	106 (23.7)	71 (21.4)	35 (30.4)	0.046
No. of patients with multiple abscesses	63 (14.1)	40 (12.0)	23 (20.0)	0.035
Free peridiverticular air	143 (32.0)	106 (31.9)	37 (32.2)	0.925
Free air in abdomen	56 (12.5)	36 (10.8)	20 (17.4)	0.252
Free fluid	90 (20.1)	61 (18.4)	29 (25.2)	0.187
Duration of hospital stay (days)†	7 (5–13)	7 (4–10)	10 (7–18)	< 0.001 [#]

Values in parentheses are percentages, unless indicated otherwise; values are *mean (s.d.) and †median (i.q.r.). ‡ Abscess 5 cm or larger in diameter and/or distant abscess. PCD, percutaneous drainage; NSAID, non-steroidal anti-inflammatory drug; § Pearson χ^2 test, except ¶ independent t test, #Mann–Whitney U test and **Fisher's exact test.

Table 2 Short- and long-term outcomes

	Total cohort (n = 447)			Hinchey Ib (n = 215)			Hinchey II* (n = 232)		
	Total (n = 447)	No PCD (n = 332)	PCD (n = 115)	P‡	No PCD (n = 197)	PCD (n = 18)	No PCD (n = 135)	PCD (n = 97)	P‡
Short-term outcomes									
Treatment failure	120 (26.8)	79 (23.8)	41 (35.7)	0.013	44 (22.3)	6 (33)	35 (25.9)	35 (36)	0.149
Complications†	25 (5.6)	13 (3.9)	12 (10.4)	0.009	8 (4.2)	0 (0)	5 (3.7)	12 (12)	0.032§
Clinical deterioration/disease progression	95 (21.3)	59 (17.8)	36 (31.3)	0.002	30 (15.2)	6 (33)	29 (21.5)	30 (31)	0.147
Readmission	71 (15.9)	49 (14.8)	22 (19.1)	0.253	27 (13.7)	5 (28)	22 (16.3)	17 (18)	0.714
Persistent diverticulitis	63 (14.1)	42 (12.7)	21 (18.3)	0.130	23 (11.7)	5 (28)	19 (14.1)	16 (16)	0.583
Emergency surgery (sigmoid resection)	40 (8.9)	24 (7.2)	16 (13.9)	0.030	10 (5.1)	1 (6)	14 (10.4)	15 (15)	0.117
Death	5 (1.1)	3 (0.9)	2 (1.7)	0.607§	3 (1.5)	0 (0)	0 (0)	2 (2)	0.332§
Long-term outcomes									
Complications†	74 (16.6)	46 (13.9)	28 (24.3)	0.009§	25 (12.7)	7 (39)	21 (15.6)	21 (22)	0.245
Overall recurrence	122 (27.3)	93 (28.0)	29 (25.2)	0.474§	54 (27.4)	7 (39)	39 (28.9)	22 (23)	0.349§
Sigmoid resection	124 (27.7)	87 (26.2)	37 (32.2)	0.07§	57 (28.9)	6 (33)	30 (22.2)	31 (32)	0.046§
Death	28 (6.3)	16 (4.8)	12 (10.4)	0.048§	8 (4.1)	2 (11)	8 (5.9)	10 (10)	0.270§

Values in parentheses are percentages. *Abscess 5 cm or larger in diameter and/or distant abscess. †Colonic obstruction/ileus, fistula or perforation. PCD, percutaneous drainage. ‡Pearson χ^2 test, except §Fisher's exact test and †Mantel-Cox log rank test.

Table 3 Multivariable logistic regression analysis of risk factors for short-term treatment failure and emergency surgery

	Odds ratio	<i>P</i>
Treatment failure		
Age (per year)	1.001 (0.98, 1.02)	0.955
BMI (per kg/m ²)	0.94 (0.89, 0.997)	0.041
Alcohol consumption	0.63 (0.36, 1.10)	0.099
Co-morbidity	1.40 (0.85, 2.29)	0.183
NSAID prescription	0.58 (0.21, 1.57)	0.242
Nausea	1.32 (0.83, 2.12)	0.245
C-reactive protein (mg/l)	1.001 (0.998, 1.003)	0.656
Abscess ≥ 3 cm	2.05 (1.09, 3.86)	0.027
Percutaneous drainage	1.47 (0.81, 2.68)	0.185
Emergency surgery		
History of abdominal surgery	2.05 (1.04, 4.05)	0.038
Rebound tenderness	2.03 (0.98, 4.21)	0.058
Abscess ≥ 5 cm	2.96 (1.08, 8.13)	0.036
Percutaneous drainage	1.29 (0.56, 2.99)	0.554

Values in parentheses are 95 per cent confidence intervals. NSAID, non-steroidal anti-inflammatory drug.

Table 4 Multivariable Cox regression analysis of risk factors for recurrence and surgery during long-term follow-up

	Hazard ratio	<i>P</i>
Recurrence		
Age (per year)	0.995 (0.98, 1.01)	0.481
History of diverticulitis	1.71 (1.17, 2.48)	0.005
History of abdominal surgery	0.63 (0.42, 0.98)	0.040
Rebound tenderness	0.72 (0.46, 1.13)	0.152
Sigmoid resection during short-term follow-up	0.15 (0.05, 0.48)	0.001
Surgery		
Age (per year)	1.02 (1.001, 1.03)	0.042
Alcohol consumption	0.64 (0.29, 1.39)	0.218
Co-morbidity	1.49 (0.96, 2.31)	0.078
History of diverticulitis	1.30 (0.88, 1.93)	0.190
Duration of symptoms (per day)	1.01 (0.996, 1.03)	0.136
Nausea	1.72 (1.03, 2.85)	0.037
Vomiting	1.82 (1.13, 2.93)	0.014
Diffuse abdominal pain	0.60 (0.29, 1.25)	0.161
Distant abscess	0.72 (0.42, 1.23)	0.221
Free peridiverticular air	1.39 (0.91, 2.12)	0.129
Percutaneous drainage	1.08 (0.69, 1.69)	0.736

Values in parentheses are 95 per cent confidence intervals.

Figures

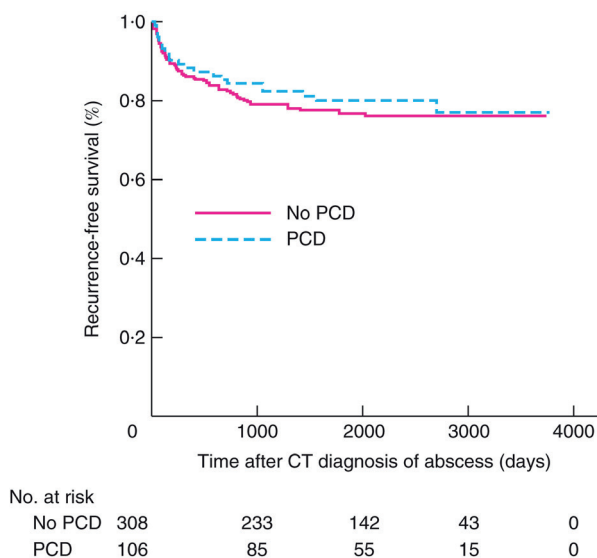


Figure 1 Kaplan–Meier analysis of recurrence-free survival according to whether the patient underwent percutaneous abscess drainage. PCD, percutaneous drainage. $P = 0.544$ (log rank test).

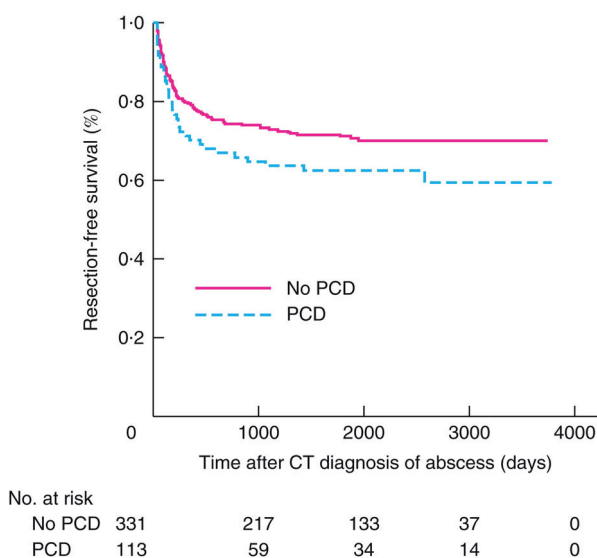


Figure 2 Kaplan–Meier analysis of resection-free survival according to whether the patient underwent percutaneous abscess drainage. PCD, percutaneous drainage. $P = 0.088$ (log rank test).

Supporting Information

Table S1 Univariable logistic regression analysis of risk factors for short-term treatment failure and emergency surgery

	Treatment failure (N=120)	Odds ratio (95%CI)	P-value	Emergency Surgery (N=40)	Odds ratio (95%CI)	P-value
Patient demographics						
Gender, N male (%)	48 (40.0%)	0.96 (0.63-1.47)	0.852	13 (32%)	0.62 (0.31-1.26)	0.189
Age in years, mean (SD)	62 (13)	1.01 (1.00-1.03)	0.140	63 (13)	1.01 (0.99-1.04)	0.397
BMI kg/m ² , mean (SD)	26.6 (5.5)	0.95 (0.89-1.01)	0.074	26.7 (6.1)	0.96 (0.85-1.08)	0.437
Smoking, N (%)	63 (52.5%)	1.10 (0.55-2.19)	0.779	23 (59%)	1.40 (0.66-2.97)	0.372
Alcohol consumption, N (%)	53 (44.2%)	0.64 (0.39-1.05)	0.074	12 (31%)	0.36 (0.14-0.88)	0.027
Comorbidities						
ASA >II, N (%)	37 (30.8%)	1.25 (0.79-1.98)	0.342	15 (38%)	1.74 (0.88-3.43)	0.113
Patients with registered comorbidity, N (%)	82 (68.3%)	1.54 (0.99-2.40)	0.058	27 (69%)	1.51 (0.74-3.06)	0.257
Medical history						
History of diverticulitis, N (%)	39 (32.5%)	1.13 (0.72-1.77)	0.600	14 (36%)	1.30 (0.65-2.59)	0.454
History of abdominal surgery, N (%)	43 (35.8%)	1.11 (0.71-1.73)	0.644	19 (49%)	1.99 (1.03-3.85)	0.042
Medication						
NSAIDs prescription, N (%)	39 (32.5%)	0.59 (0.27-1.27)	0.159	8 (21%)	0.34 (0.12-1.01)	0.052
Steroids prescription, N (%)	9 (7.5%)	0.67 (0.30-1.52)	0.337	3 (8%)	0.70 (0.19-2.60)	0.596
Clinical symptoms						
N days of symptoms, median (IQR)	7 (3-13)	1.00 (0.98-1.02)	0.950	10 (4-18)	1.02 (1.00-1.05)	0.058
Nausea, N (%)	71 (60.2%)	1.43 (0.89-2.30)	0.134	28 (72%)	2.40 (1.13-5.10)	0.023
Vomiting, N (%)	29 (24.2%)	0.97 (0.55-1.72)	0.916	12 (31%)	1.35 (0.57-3.23)	0.490
Diffuse abdominal pain, N (%)	15 (12.5%)	0.90 (0.39-2.06)	0.798	4 (10%)	0.71 (0.13-3.95)	0.680
Change in bowel habit, N (%)	78 (65.0%)	0.98 (0.59-1.63)	0.928	26 (67%)	1.08 (0.40-2.95)	0.869
Rectal blood loss, N (%)	20 (16.7%)	1.12 (0.61-2.07)	0.710	8 (21%)	1.47 (0.59-3.70)	0.408
Clinical signs						
Rebound tenderness, N(%)	38 (31.7%)	0.99 (0.59-1.68)	0.983	18 (46%)	2.08 (1.02-4.23)	0.043
Local muscular guarding/resistance, N (%)	35 (32.1%)	1.24 (0.76-2.05)	0.394	11 (28%)	1.14 (0.51-2.56)	0.745
Diffuse muscular guarding, N (%)	14 (11.7%)	1.08 (0.45-2.56)	0.858	4 (10%)	0.90 (0.19-4.19)	0.885
Temperature degrees Celsius, mean (SD)	37.8 (0.9)	1.11 (0.84-1.47)	0.436	37.9 (0.9)	1.31 (0.89-1.91)	0.171

	Treatment failure (N=120)	Odds ratio (95%CI)	P-value	Emergency Surgery (N=40)	Odds ratio (95%CI)	P-value
Laboratory parameters						
CRP mg/L, mean (SD)	179 (117)	1.001 (1.00-1.003)	0.183	204 (104)	1.003 (1.000-1.006)	0.037
WBC x10 ⁹ /L, mean (SD)	15.1 (5.2)	1.02 (0.97-1.06)	0.492	15.5 (6.3)	1.03 (0.96-1.10)	0.455
Radiological parameters						
Hinchey II*, N (%)	70 (58.3%)	1.44 (0.88-2.37)	0.147	27 (69%)	2.40 (1.04-5.54)	0.040
Largest abscess diameter (cm), median (IQR)	4.8 (3.2-6.3)	1.08 (1.00-1.17)	0.051	5.6 (4.2-7.8)	1.20 (1.08-1.35)	0.001
Location abscess distant, N (%)	26 (21.7%)	0.85 (0.52-1.41)	0.530	8 (21%)	0.81 (0.36-1.83)	0.619
Multiple abscesses present, N (%)	16 (13.3%)	0.92 (0.50-1.69)	0.780	7 (41%)	1.38 (0.58-3.27)	0.471
Free air peridiverticular, N (%)	34 (28.3%)	0.88 (0.55-1.43)	0.461	10 (26%)	0.69 (0.31-1.57)	0.376
Free air abdomen, N (%)	16 (13.3%)	1.09 (0.47-2.53)	0.843	4 (10%)	0.74 (0.13-4.24)	0.714
Free fluid, N (%)	23 (19.2%)	0.92 (0.47-1.81)	0.801	9 (23%)	1.17 (0.50-2.77)	0.714
Treatment						
Antibiotics only, N (%)	79 (65.8%)	0.56 (0.36-0.89)	0.014	24 (60%)	0.48 (0.25-0.94)	0.033
Percutaneous abscess drainage, N (%)	41 (34.2%)	1.77 (1.12-2.80)	0.014	16 (40%)	2.07 (1.06-4.06)	0.033

*Hinchey 2 is defined as abscess ≥ 5 centimeter in diameter and/or distant abscess

Abbreviations: N= number, CI= confidence interval, SD = standard deviation, BMI= Body Mass Index, ASA= American Society of Anesthesiologists, NSAIDs= non-steroidal anti-inflammatory drugs, IQR= inter quartile range, CRP = C-reactive protein, WBC= white blood cell count

Table S2 Univariable Cox regression analysis of risk factors for recurrence and surgery in long-term follow-up

	Recurrence (N=122)	Hazard ratio (95%CI)	P-value	Surgery (N=124)	Hazard ratio (95%CI)	P-value
Patient demographics						
Gender, N male (%)	54 (44.3%)	1.16 (0.81-1.66)	0.407	48 (38.7%)	0.86 (0.72-1.04)	0.860
Age in years, mean (SD)	59 (13)	0.99 (0.98-1.00)	0.084	62 (12)	1.01 (1.01-1.02)	0.053
BMI kg/m ² , mean (SD)	28.1 (5.7)	1.01 (0.96-1.05)	0.821	28.2 (5.9)	1.00 (0.97-1.04)	0.886
Smoking, N (%)	64 (52.5%)	1.09 (0.74-1.61)	0.664	65 (52.4%)	1.12 (0.65-1.94)	0.657
Alcohol consumption, N (%)	61 (50.0%)	0.90 (0.57-1.41)	0.632	57 (46.0%)	0.65 (0.36-1.17)	0.135
Comorbidities						
ASA >II, N (%)	32 (26.2%)	0.95 (0.64-1.43)	0.819	35 (28.2%)	1.17 (0.96-1.43)	0.423
Patients with registered comorbidity, N (%)	75 (61.5%)	1.08 (0.75-1.56)	0.665	85 (68.5%)	1.61 (1.10-2.36)	0.014
Medical history						
History of diverticulitis, N (%)	46 (37.7%)	1.51 (1.04-2.18)	0.030	41 (33.1%)	1.29 (0.89-1.88)	0.177
History of abdominal surgery, N (%)	30 (24.6%)	0.60 (0.40-0.91)	0.016	44 (35.5%)	1.16 (0.80-1.69)	0.429
Medication						
NSAIDs prescription, N (%)	61 (50.0%)	1.52 (0.71-3.24)	0.242	53 (42.7%)	0.97 (0.39-2.42)	0.942
Steroids prescription, N (%)	15 (12.3%)	1.44 (0.76-2.73)	0.263	9 (7.3%)	0.70 (0.32-1.50)	0.352
Clinical symptoms						
N days of symptoms, median (IQR)	7 (3-13)	0.998 (0.98-1.02)	0.841	7 (4-15)	1.01 (1.00-1.03)	0.095
Nausea, N (%)	68 (55.7%)	1.16 (0.79-1.70)	0.454	81 (65.3%)	2.18 (1.41-3.37)	0.001
Vomiting, N (%)	34 (27.9%)	1.24 (0.83-1.85)	0.293	47 (37.9%)	2.42 (1.64-3.58)	<0.001
Diffuse abdominal pain, N (%)	12 (9.8%)	0.63 (0.25-1.56)	0.297	13 (10.5%)	0.63 (0.34-1.19)	0.156
Change in bowel habit, N (%)	80 (65.6%)	0.99 (0.62-1.57)	0.949	83 (66.9%)	1.04 (0.50-2.18)	0.904
Rectal blood loss, N (%)	22 (18.0%)	1.21 (0.72-2.03)	0.467	17 (13.7%)	1.02 (0.57-1.84)	0.953
Clinical signs						
Rebound tenderness, N(%)	31 (25.4%)	0.71 (0.46-1.12)	0.140	30 (24.2%)	0.72 (0.42-1.25)	0.237
Local muscular guarding/resistance, N (%)	29 (23.8%)	0.88 (0.55-1.41)	0.598	30 (24.2%)	0.94 (0.59-1.48)	0.784
Diffuse muscular guarding, N (%)	16 (13.1%)	1.26 (0.72-2.23)	0.418	16 (12.9%)	1.09 (0.39-3.08)	0.852
Temperature degrees Celsius, mean (SD)	37.8 (0.9)	1.11 (0.91-1.34)	0.309	37.7 (1.0)	0.98 (0.78-1.23)	0.845

	Recurrence (N=122)	Hazard ratio (95%CI)	P-value	Surgery (N=124)	Hazard ratio (95%CI)	P-value
Laboratory parameters						
CRP mg/L, mean (SD)	161 (111)	0.999 (0.997-1.001)	0.437	159 (97)	0.999 (0.998-1.001)	0.469
WBC x10 ⁹ /L, mean (SD)	14.7 (5.5)	0.99 (0.96-1.03)	0.660	14.4 (5.6)	0.98 (0.94-1.02)	0.369
Radiological parameters						
Hinchey II*, N (%)	61 (50.0%)	0.93 (0.64-1.35)	0.696	60 (48.4%)	0.95 (0.65-1.38)	0.777
Largest abscess diameter (cm), median (IQR)	4.1 (2.7-6.0)	0.97 (0.89-1.06)	0.473	4.4 (2.8-6.2)	1.04 (0.97-1.11)	0.313
Location abscess distant, N (%)	25 (20.5%)	0.84 (0.54-1.30)	0.438	23 (18.5%)	0.72 (0.45-1.13)	0.147
Multiple abscesses present, N (%)	19 (15.6%)	1.14 (0.70-1.87)	0.594	19 (15.3%)	1.17(0.91-1.50)	0.527
Free air peridiverticular, N (%)	35 (28.7%)	0.82 (0.51-1.32)	0.409	47 (37.9%)	1.29 (0.88-1.90)	0.193
Free air abdomen, N (%)	15 (12.3%)	0.99 (0.57-1.73)	0.972	17 (13.7%)	1.05 (0.40-2.76)	0.910
Free fluid, N (%)	22 (18.0%)	0.85 (0.52-1.38)	0.509	24 (19.4%)	1.05 (0.66-1.67)	0.838
Treatment						
Antibiotics only, N (%)	93 (76.2%)	1.13 (0.75-1.72)	0.557	87 (70.2%)	0.70 (0.48-1.01)	0.065
Percutaneous abscess drainage, N (%)	29 (23.8%)	0.88 (0.58-1.34)	0.557	37 (29.8%)	1.44 (0.99-2.08)	0.065
Sigmoid resection	3 (2.5%)	0.16 (0.05-0.52)	0.002	0 (0%)	N/A	N/A

*Hinchey 2 is defined as abscess ≥ 5 centimeter in diameter and/or distant abscess

Abbreviations: N= number, CI= confidence interval, SD= standard deviation, BMI= Body Mass Index, ASA= American Society of Anesthesiologists, NSAIDs= non-steroidal anti-inflammatory drugs, IQR= inter quartile range, CRP = C-reactive protein, WBC= white blood cell count

Table S3 Sensitivity analyses of short- and long-term outcomes

	Total (N=447)	No PCD (N=332)	PCD (N=115)	P-value	Hospital Adjusted P-value	P-value NI
Short-term outcomes						
Treatment failure	120 (26.8%)	79 (23.8%)	41 (35.6%)	0.013 ²	0.038	0.007 ²
Complications**	25 (5.6%)	13 (3.9%)	12 (10.4%)	0.009 ²	0.122	0.009 ²
Clinical deterioration/disease progression	95 (21.3%)	59 (17.8%)	36 (31.3%)	0.002 ²	0.040	0.002 ²
Readmission	71 (15.9%)	49 (14.8%)	22 (19.1%)	0.253 ²	0.720	0.253 ²
Persistent diverticulitis	63 (14.1%)	42 (12.7%)	21 (18.3%)	0.130 ²	0.234	0.130 ²
Emergency surgery (sigmoid resection)	40 (8.9%)	24 (7.2%)	16 (13.9%)	0.030 ²	0.069	0.030 ²
Mortality	5 (1.1%)	3 (0.9%)	2 (1.7%)	0.607 ¹	0.811	0.465 ²
Long-term outcomes						
Complications**	74 (16.6%)	46 (13.9%)	28 (24.3%)	0.009 ¹	N/A	0.013 ¹
Overall recurrence	122 (27.2%)	93 (28.0%)	29 (25.2%)	0.474 ³	N/A	0.545 ³
Sigmoid resection	124 (27.7%)	87 (26.2%)	37 (32.2%)	0.073 ³	N/A	0.080 ³
Mortality	28 (6.3%)	16 (4.8%)	12 (10.4%)	0.048 ³	N/A	0.047 ³

¹Fisher's exact test ²Pearson's Chi-square test ³Mantel-Cox log-rank test

**Development of colonic obstruction/ileus, fistula, or perforation

Data are n (%)

Abbreviations: PCD = percutaneous abscess drainage, NI = non-impacted dataset, N/A = not applicable

Table S4 Sensitivity analyses of short- and long-term outcomes in Hinchey IB and II patients

Hinchey IB	No PCD (N=197)	PCD (N=18)	P-value	P-value adjusted for hospital	P-value NI
Short-term outcomes					
Treatment failure	44 (22.3%)	6 (33%)	0.359 ¹	0.064	0.112 ¹
Complications**	8 (4.1%)	0 (0%)	0.908 ¹	0.818	1.000 ¹
Clinical deterioration/disease progression	30 (15.2%)	6 (33%)	0.091 ¹	0.023	0.030 ¹
Readmission	27 (13.7%)	5 (28%)	0.178 ¹	0.279	0.030 ¹
Persistent diverticulitis	23 (11.7%)	5 (28%)	0.100 ¹	0.064	0.015 ¹
Emergency surgery (sigmoid resection)	10 (5.1%)	1 (6%)	0.693 ¹	0.663	1.000 ¹
Mortality	3 (1.5%)	0 (0%)	1.000 ¹	0.876	1.000 ¹
Long-term outcomes					
Complications**	25 (12.7%)	7 (39%)	0.016 ¹	N/A	0.017 ¹
Overall recurrence	54 (27.4%)	7 (39%)	0.623 ³	N/A	0.207 ³
Sigmoid resection	57 (28.9%)	6 (33%)	0.474 ³	N/A	0.642 ³
Mortality	8 (4.1%)	2 (11%)	0.263 ³	N/A	0.071 ³
Hinchey II*	No PCD (N= 135)	PCD (N=97)	P-value	P-value adjusted for hospital	P-value NI
Short-term outcomes					
Treatment failure	35 (25.9%)	35 (36%)	0.149 ²	0.683	0.355 ¹
Complications**	5 (3.7%)	12 (12%)	0.032 ¹	0.181	0.066 ¹
Clinical deterioration/disease progression	29 (21.5%)	30 (31%)	0.147 ²	0.731	0.440 ²
Readmission	22 (16.3%)	17 (18%)	0.714 ²	0.442	0.547 ¹
Persistent diverticulitis	19 (14.1%)	16 (16%)	0.583 ²	0.792	0.581 ¹
Emergency surgery (sigmoid resection)	14 (10.4%)	15 (15%)	0.117 ²	0.293	0.258 ¹
Mortality	0 (0%)	2 (2%)	0.332 ¹	0.736	0.208 ²
Long-term outcomes					
Complications**	21 (15.6%)	21 (22%)	0.245 ²	N/A	0.183 ²
Overall recurrence	39 (28.8%)	22 (22.7%)	0.349 ³	N/A	0.973 ³
Sigmoid resection	30 (22.2%)	31 (32%)	0.046 ³	N/A	0.016 ³
Mortality	8 (5.9%)	10 (10%)	0.270 ³	N/A	0.636 ³

¹Fisher's exact test ²Pearson's Chi-square test ³Mantel-Cox log-rank test

*Hinchey II is defined as abscess ≥5 centimeter in diameter and/or distant abscess

**Development of colonic obstruction/ileus, fistula, or perforation

Data are n (%)

Abbreviations: PCD = percutaneous abscess drainage, NI = non-imputed dataset, N/A = not applicable

Table S5 Sensitivity analysis multivariable logistic regression (short-term)

Treatment failure		Unadjusted		Adjusted for hospital		NI
Variable	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	P-value	P-value
Age (years)	1.001 (0.98-1.02)	0.955	1.000 (0.98-1.02)	0.987	N/A*	N/A*
BMI (kg/m ²)	0.94 (0.89-0.997)	0.041	0.93 (0.88-0.99)	0.018	N/A*	N/A*
Alcohol consumption	0.63 (0.36-1.10)	0.099	0.73 (0.38-1.42)	0.343	N/A*	N/A*
Comorbidity	1.40 (0.85-2.29)	0.183	1.39 (0.83-2.33)	0.215	N/A*	N/A*
NSAID prescription	0.58 (0.21-1.57)	0.242	0.62 (0.18-2.11)	0.403	N/A*	N/A*
Nausea	1.32 (0.83-2.12)	0.245	1.28 (0.75-2.20)	0.365	N/A*	N/A*
CRP (mg/L)	1.001 (0.998-1.003)	0.656	1.00 (0.997-1.003)	0.916	N/A*	N/A*
Abscess ≥ 3cm	2.05 (1.09-3.86)	0.027	2.16 (1.11-2.30)	0.024	N/A*	N/A*
Percutaneous drainage	1.47 (0.81-2.68)	0.185	1.28 (0.71-2.30)	0.416	N/A*	N/A*
Emergency Surgery		Unadjusted		Adjusted for hospital		NI
Variable	Odds ratio (95%CI)	P-value	Odds ratio (95%CI)	P-value	P-value	P-value
History of abdominal surgery	2.05 (1.04-4.05)	0.038	2.11 (1.04-4.27)	0.039	0.127	0.127
Rebound tenderness	2.03 (0.98-4.21)	0.058	2.18 (1.04-4.55)	0.038	0.093	0.093
Abscess ≥ 5cm	2.96 (1.08-8.13)	0.036	2.98 (1.06-8.43)	0.040	0.003	0.003
Percutaneous drainage	1.29 (0.56-2.99)	0.554	1.14 (0.47-2.78)	0.772	0.248	0.248

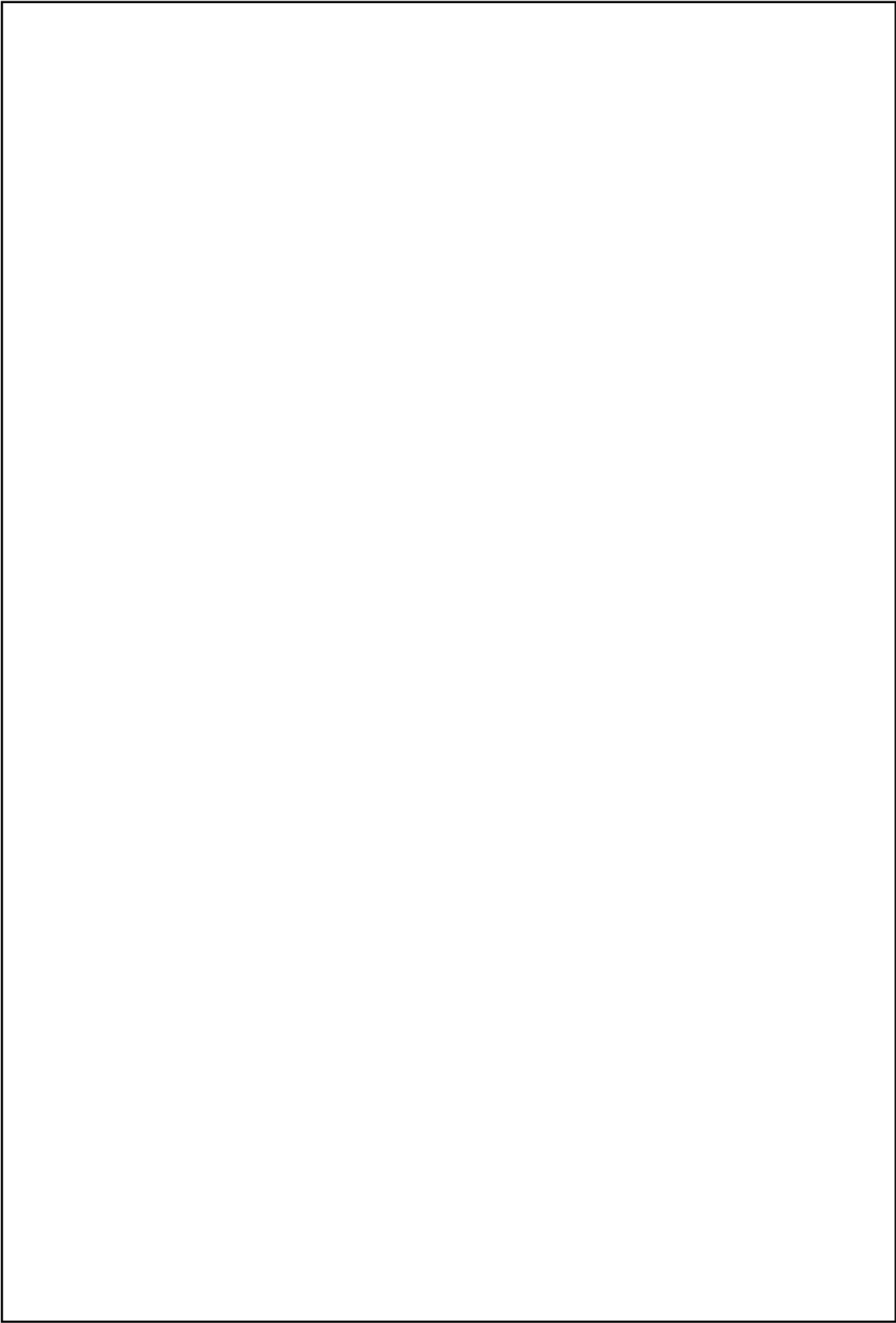
Abbreviations: CI= confidence interval, BMI = Body Mass Index, NSAIDs= non-steroidal anti-inflammatory drugs, CRP = C-reactive protein, ASA= American Society of Anesthesiologists, NI=non-imputed dataset N/A= not applicable

*too many missing variables for multiple logistic regression

Table S6 Sensitivity analysis Cox regression (long-term)

Variable	Unadjusted		Adjusted for hospital		NI
	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value	
Recurrence					
Age in years	0.995 (0.98-1.01)	0.481	0.996 (0.98-1.01)	0.547	0.984
History of diverticulitis	1.71 (1.17-2.48)	0.005	1.77 (1.21-2.60)	0.003	0.009
History of abdominal surgery	0.63 (0.42-0.98)	0.040	0.63 (0.41-0.97)	0.052	0.024
Rebound tenderness	0.72 (0.46-1.13)	0.152	0.71 (0.44-1.15)	0.166	0.146
Sigmoid resection in short term follow-up	0.15 (0.05-0.48)	0.001	0.16 (0.05-0.51)	0.002	0.017
Surgery					
Variable	Hazard ratio (95%CI)	P-value	Hazard ratio (95%CI)	P-value	P-value
Age in years	1.02 (1.001-1.03)	0.042	1.02 (1.002-1.03)	0.026	0.579
Alcohol consumption	0.64 (0.29-1.39)	0.218	0.54 (0.30-0.98)	0.043	0.593
Comorbidity	1.49 (0.96-2.31)	0.078	1.49 (0.96-2.33)	0.077	0.153
History of diverticulitis	1.30 (0.88-1.93)	0.190	1.50 (0.99-2.27)	0.058	0.803
Days symptoms	1.01 (0.996-1.03)	0.136	1.01 (0.99-1.03)	0.187	0.510
Nausea	1.72 (1.03-2.85)	0.037	1.72 (1.06-2.78)	0.028	0.190
Vomiting	1.82 (1.13-2.93)	0.014	1.67 (1.00-2.79)	0.051	0.891
Diffuse abdominal pain	0.60 (0.29-1.25)	0.161	0.52 (0.25-1.05)	0.069	0.552
Distant abscess	0.72 (0.42-1.23)	0.221	0.74 (0.41-1.35)	0.321	0.281
Free air peridiverticular	1.39 (0.91-2.12)	0.129	1.41 (0.89-2.22)	0.141	0.552
Percutaneous abscess drainage	1.08 (0.69-1.69)	0.736	0.92 (0.58-1.47)	0.731	0.890

Abbreviations: CI= confidence interval NI= non-imputed dataset



Chapter 3

Long-term follow-up of a multicentre cohort study on laparoscopic peritoneal lavage for perforated diverticulitis

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Abstract

Aim

Laparoscopic peritoneal lavage has increasingly been investigated as a promising alternative to sigmoidectomy for perforated diverticulitis with purulent peritonitis. Most studies only reported outcomes up to 12 months. Therefore, the objective of this study was to evaluate long-term outcomes of patients treated with laparoscopic lavage.

Methods

Between 2008 and 2010, 38 patients treated with laparoscopic lavage for perforated diverticulitis in 10 Dutch teaching hospitals were included. Long-term follow-up data on patient outcomes, e.g. diverticulitis recurrence, reoperations and readmissions, were collected retrospectively. The characteristics of patients with recurrent diverticulitis or complications requiring surgery or leading to death, categorized as 'overall complicated outcome', were compared with patients who developed no complications or complications not requiring surgery.

Results

The median follow-up was 46 months (interquartile range: 7-77), during which 17 episodes of recurrent diverticulitis (seven complicated) in 12 patients (32%) occurred. Twelve patients (32%) required additional surgery with a total of 29 procedures. Fifteen patients (39%) had a total of 50 readmissions. Of initially successfully treated patients (n=31), twelve (31%) had recurrent diverticulitis or other complications. At 90 days, 32 (84%) patients were alive without undergoing a sigmoidectomy. However, seven (22%) of these patients eventually had a sigmoidectomy after 90 days. Diverticulitis-related events occurred up to six years after the index procedure.

Conclusion

Long-term diverticulitis recurrence, reintervention and readmission rates after laparoscopic lavage were high. A complicated outcome was also seen in patients who had initially been treated successfully with laparoscopic lavage with relevant events occurring up to 6 years after initial surgery.

What does this paper add to the literature?

Laparoscopic lavage for perforated diverticulitis has increasingly been investigated, but long-term data were scarce. With a median follow-up of 46 months, this paper reports on long-term outcomes after laparoscopic lavage and shows long-term diverticulitis recurrence, reintervention and readmission rates after laparoscopic lavage to be high.

Introduction

Diverticular disease is a common problem in developed countries, resulting in an estimated annual rate of up to 786,000 hospital admissions in Europe (1). Of patients with acute diverticulitis 8%-35% present with abscess formation or peritonitis (modified Hinchey grade Ib-IV), resulting in an estimated 60,000 perforated diverticulitis cases per year in Europe (1-5). Perforated diverticulitis with generalized peritonitis requires surgical treatment in most cases. Nevertheless, both the Hartmann's procedure (HP) and sigmoidectomy with primary anastomosis (PA) have been associated with significant morbidity and mortality rates (6-8). Therefore, after its introduction in 1996, laparoscopic peritoneal lavage (LL) has increasingly been investigated as a promising alternative to sigmoidectomy (9-17). Despite initial promising results, recent randomized controlled trials showed increased rates of severe postoperative complications and reoperations compared with sigmoidectomy (18-23).

Current studies on LL predominantly report on outcomes up to 12 months after surgery (13, 14, 16, 17, 24-26). Reports on the long-term consequences of LL as therapy for perforated diverticulitis are scarce (27-29). Therefore, further exploration of long-term outcomes is of importance, since leaving the diseased colonic segment *in situ* after LL potentially puts patients at increased risk for both uncomplicated and complicated diverticulitis recurrence, which might necessitate surgery (3, 19, 23). Additionally, long-term outcomes of patients treated with LL potentially could provide relevant insights into which patients might benefit most from this treatment (26).

Therefore, the aim of this study was to assess the long-term outcomes of a previously published cohort study of patients treated with LL for perforated diverticulitis, with regard to diverticulitis recurrence, subsequent related complications, and surgical interventions (25).

Methods

A multicentre, retrospective cohort study was performed. The study was approved by the institutional review boards of all participating hospitals. Due to the retrospective design, informed consent was waived for participation in this study. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) recommendations for reporting of observational studies were followed (30). Detailed methods of the short-term follow-up of this study were published previously by Swank *et al.* (25).

Patient inclusion

Patients treated with LL for perforated diverticulitis in 10 Dutch teaching hospitals between 1 January 2008 and 31 December 2010 were included (25). Patient records were screened for the diagnosis 'diverticulitis' or 'acute abdomen' and subsequently operation type was recorded. Patients who underwent LL as primary treatment for complicated diverticulitis with either free air and/or purulent peritonitis were included.

Data collection: short-term follow-up

Baseline patient demographics, such as co-morbidities, American Society of Anesthesiologists (ASA) score, preoperative white blood cell (WBC) count, C-reactive protein (CRP) and the results of preoperative X-ray or computed tomography (CT) scan were recorded previously. Furthermore, operative records were screened, and short-term recurrent diverticulitis, numbers and types of complications, diagnostic measures, re-interventions and readmissions were recorded.

Data collection: long-term follow-up

In the present study, additional long-term data collection was performed through retrospective review of patient records. All events are reported jointly in this study. Short-term follow-up was defined as the first 90 days after index surgery; long-term follow-up consisted of the period thereafter. During long-term follow-up, patient records were screened for survival status, readmissions, re-interventions, complicated or uncomplicated diverticulitis recurrence, development of fistulas, intra-abdominal abscesses, colonic stenosis, or other potentially related complications, as well as colonoscopies and abdominal CT scans, diagnosis of colorectal malignancies (e.g. rectosigmoid) and midline incisional or parastomal hernias.

Outcome parameters

Primary treatment failure of LL was defined as ongoing abdominal sepsis. Long-term outcomes of patients without a sigmoidectomy at 90 days of follow-up after the index procedure were assessed. The modified Hinchey classification was used to categorize patients according to the intra-operative findings (5). The Mannheim Peritonitis Index was used as predictor of the mortality risk (31). Recurrent diverticulitis episodes were classified as either uncomplicated or complicated based on the information available from patient records. Diverticulitis episodes were classified as complicated when associated with perforation, abscess formation, fistulas, stenosis or diverticular bleeding (32). Clinical follow-up was calculated as the time between the index admission and the last recorded hospital visit and, additionally, total study follow-up was calculated as the

time between the index admission and the time of data extraction by the researcher (D.S. or D.L.). ‘Overall complicated outcome’ was defined as postoperative complications or recurrent diverticulitis requiring surgery or resulting in mortality. To identify potential risk factors for an overall complicated outcome during follow-up, patients with and without a complicated outcome were compared.

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics (Version 24, IBM, Armonk, NY, USA). Continuous variables were presented as medians with interquartile range (IQR) or means with standard deviation (\pm SD), depending on normality of data. Discrete variables were presented as numbers (n) with percentages (%). Depending on the data distribution a Student’s t-test or Mann-Whitney U test, as appropriate, was used for comparison of continuous variables. Fisher’s exact test was used for comparing discrete variables with two categories and a Chi-squared test for discrete variables with three or more categories. A P value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Medical records were screened for potentially eligible patients in 34 Dutch hospitals. Eventually, from 10 of these hospitals, 38 patients were included who were treated for Hinchey grade II or III diverticulitis by means of LL. Baseline characteristics are summarized in Table 1 and were previously described by Swank *et al.* (25). One or more co-morbidities were present in 18 patients, consisting of cardiovascular disease (n=8), previously diagnosed malignant disease (n=5), hypertension (n=3) and chronic obstructive pulmonary disease (COPD) (n=2). None of the included patients had a previous episode of diverticulitis, two patients had previous abdominal surgery not related to diverticular disease, and one patient suffered from respiratory insufficiency before the LL procedure.

Overall outcomes

Short-term (<90 days) and long-term follow-up are summarized in Table 2-4 and Fig. 1. The number of recurrent diverticulitis episodes and surgical reinterventions for 1-, 3- and 5-year intervals as well as until the end of follow-up are presented in Table 5. Patient records were examined after a median of 90 months (84-96). Median clinical follow-up, as defined earlier, was 46 months (7-77). During the entire follow-up period, 27 (71%) patients had at least one adverse event. In 12 patients (32%), 17 recurrent episodes of diverticulitis (seven complicated and 10 uncomplicated) were reported. The median time between LL and first recurrence of diverticulitis was 341 days (range 61-2119, IQR 115-795). Recurrence-free survival is presented in Fig. 2. The median time to sigmoidectomy was 240 days (range 2-1406); resection-free survival is shown in Fig. 3. Twenty-nine subsequent surgical procedures among 12 patients (32%) were reported, of whom seven had emergency surgery at least once. In total, four patients (11%) died due to causes related to or as a direct consequence of their diverticular disease, including multiple organ failure (n=2), persisting ileus (n=1), and aspiration pneumonia (n=1).

Four patients died due to unrelated causes: breast cancer (n=1), retroperitoneal bleeding (n=1), brain tumour (n=1), and cardiovascular disease (n=1). At least one follow-up colonoscopy or sigmoidoscopy (n=25) or CT scan (n=23) was performed in 31 patients. Extensive diverticulosis was reported in 19 (61%) of these patients. One patient was diagnosed with rectal cancer during follow-up.

Follow-up in patients with initially controlled abdominal sepsis

LL succeeded in controlling the abdominal sepsis in 31 patients. During short-term follow-up, one patient had emergency surgery for repair of a fascial dehiscence. Although abdominal sepsis was controlled, one patient died due to a persisting obstructive ileus 27 days after the index procedure. This patient was diagnosed with terminal lung cancer and it therefore was decided not to perform further surgery.

At long-term follow-up, 30 out of 31 patients successfully treated with LL were alive. Eleven of these patients (36.7%) developed either a recurrent episode of diverticulitis or other complications and six patients (20%) required additional surgery. These patients were diagnosed with recurrent complicated diverticulitis (n=5), recurrent uncomplicated diverticulitis (n=4), obstructive ileus (n=3), intra-abdominal abscesses (n=6), fistula formation (n=3), midline incisional hernia (n=2), parastomal hernia (after sigmoidectomy) (n=2) and wound infection (n=1). Additional surgical interventions for these patients consisted of sigmoidectomy (n=5), low anterior resection (n=1), end colostomy construction (n=1), obstructive ileus relief (n=2), fistulotomy with simultaneous abscess drainage (n=1), parastomal hernia repair (n=1) and stoma reversal (n=4).

Follow-up in patients with initial failure of laparoscopic lavage

LL did not succeed in controlling abdominal sepsis in seven patients. All these patients developed complications requiring surgery or died from related causes. During short-term follow-up, five patients underwent one or more surgical procedures: sigmoidectomy (n=3), loop ileostomy construction (n=1), repair of a perforated sigmoid (n=1), 2 surgical abscess drainages (n=1), and repair of fascial dehiscence (n=1). Two patients required, but could not undergo, emergency laparotomy due to their deteriorating condition. Both patients died after the index procedure due to multiple organ failure after 5 and 37 days, respectively.

At long-term follow-up five out of seven patients, who initially were unsuccessfully treated with LL, were alive. Four of these patients developed either a recurrent episode of diverticulitis or other complications and were subsequently operated upon - recurrent complicated diverticulitis (n=1), recurrent uncomplicated diverticulitis (n=1), fistula formation (n=2), or obstructive ileus (n=1). Additional surgical interventions consisted of incisional hernia repair (n=2), surgical excision of an ileosigmoid fistula (n=1), and stoma reversal (n=3). One patient died due to aspiration pneumonia following ileostomy reversal.

Follow-up in patients without sigmoidectomy at 90 days

At 90 days after the index procedure, 32 (84%) patients were still alive and did not have an initial sigmoidectomy. A total of 15 recurrent episodes of diverticulitis were reported among ten (31%) of these patients, of which 5 patients had a complicated recurrence. Of these, 7 (22%) underwent further surgery, 6 patients underwent a sigmoidectomy and 1 patient received a wedge excision of the sigmoid colon. Indications for surgery were recurrent diverticulitis (n=5), obstructive ileus (n=1), and sigmoid perforation (n=1). Other procedures in these 7 patients were relief of obstructive ileus (n=2), repair of parastomal hernia (n=1) and stoma reversal (n=5). A stoma was constructed in six of these patients (three loop ileostomies and three end colostomies).

Univariate analysis

Results of the univariate analysis are given in Table 6. Baseline characteristics of patients with an overall complicated follow-up were compared with patients that developed no complications or complications not requiring surgery. Primary treatment failure (OR 3.9, 95% CI 2.13-7.04, P=0.001) was associated with a complicated outcome. Additionally, multiple (≥ 2) preoperative co-morbidities (OR 5.43, 95% CI 1.24-23.90; P=0.033) and ASA ≥ 3 (OR 7.2, 95%CI 1.67-31.03, P=0.008) were correlated with a complicated outcome. Median CRP appeared to be higher in those patients with an overall complicated outcome. However, no statistically significant difference was found (172 mmol/L [IQR: 50-275] *vs* 242 mmol/L [IQR: 128.5-323], p=0.068).

Discussion

The present retrospective cohort study evaluated the long-term outcomes of 38 patients treated with LL for perforated diverticulitis in 10 centres in the Netherlands. Although the initial results in this patient cohort were promising, during long-term follow-up a significant number of patients had subsequent recurrent diverticulitis or developed other related complications with relevant events occurring up to 6 years after initial surgery. In patients with an initially successful outcome, complications and subsequent surgery frequently occurred.

In our study, nine patients (24%) underwent sigmoidectomy during follow-up. In previous reports on long-term outcomes after LL, sigmoidectomy rates of 44.7% and 21% were reported (28, 29). In the cohort presented by White *et al.* (28), 44.7% of patients underwent sigmoidectomy. However, eight LL patients received a planned sigmoidectomy before severe symptoms of recurrence were present. These eight patients potentially resulted in an overestimate of the sigmoidectomy rate. In our cohort there was no intention to treat patients by elective sigmoidectomy unless otherwise indicated during follow-up. The sigmoidectomy rate reported at two-year follow-up in the DILALA-trial was 21% (n=43) (14, 29). In the recently published LLO Study, the overall reoperation rate was 26% (56/212 patients) (33). Furthermore, the recurrence rate was 27% (47/172 patients) in patients without re-interventions during admission and the first 60 postoperative days. Both studies present results comparable to the

present cohort; however, follow-up in these studies was shorter, and therefore reported event rates may still increase.

A potential major advantage of LL for the treatment of perforated diverticulitis is the avoidance of HP with construction of an end colostomy or PA with a loop ileostomy, especially, since after HP colostomies may be reversed in only 50-60% of patients (34, 35). In our cohort, 32 (84%) patients were alive without undergoing a sigmoidectomy at 90 days. Overall, a stoma could be avoided in the majority (76%) of patients and most patients who did receive an end colostomy or loop ileostomy eventually had their stoma reversed (78%).

Leaving the diseased colonic segment *in situ* puts patients potentially at increased risk for both uncomplicated and complicated diverticulitis, which might necessitate surgery (19, 23). A complicated outcome was present in 26% of patients who initially had been successfully treated with LL. Seven out of 32 had recurrent complaints necessitating six sigmoidectomies and one wedge incision (22%) at long-term follow-up. Therefore, controlling the abdominal sepsis after LL does not guarantee favourable long-term outcomes. In addition, as shown in the present study, ongoing abdominal sepsis after LL is predictive of an overall complicated outcome during both short-term and long-term follow-up. In those cases, early sigmoidectomy may be necessary. Although the present study does not provide enough evidence to draw a definitive conclusion, it raises the question as to whether planned sigmoidectomies to avoid long-term sequelae should be considered during the follow-up of patients fit for surgery.

Considering the additional events during long-term follow-up, both high ASA scores (≥ 3) and the presence of two or more comorbidities, regardless of their nature or treatment, were associated with an unfavourable prognosis. This is largely in accordance with two previous studies identifying risk factors for the failure of LL (26, 33). Due to the relatively small sample size, multivariate analysis was not performed in this study. High preoperative CRP values have previously been associated with negative outcomes and increased histologic damage to the colon in patients with diverticulitis (36, 37). Therefore, it is conceivable that high preoperative CRP levels might have some predictive value for overall unfavourable outcomes after LL. Although median CRP appeared to be higher in those patients with an overall complicated outcome, this association was not confirmed in the current study.

This study has several limitations of which most are inherent to its retrospective observational design. The study cohort is at risk for selection bias, as the decision to treat patients with LL was made clinically. At the time of patient inclusion, patients with a more favourable prognosis might have been selected more often to undergo this treatment. Furthermore, no control patients undergoing primary resection were included in this cohort to compare long-term results of both treatment strategies. Additionally, the retrospective study design might have led to heterogenic and potentially incomplete follow-up, which could underestimate the number of adverse events. Nevertheless, despite this, the event rate was still considerable. Finally, given the small sample size of this study, the results should be interpreted with caution.

To date, three randomized studies and several subsequent meta-analyses comparing laparoscopic peritoneal lavage to primary resection have been published (16, 17, 19-24, 38). However, three of these meta-analyses are criticized as having methodological errors and provide discrepant conclusions (39). Therefore, effectiveness of LL remains a topic for debate. Two meta-analyses reported increased re-operation and morbidity rates in LL patients at 3 months, whereas, at 12 months the reoperation rate was reported to be higher in the primary resection patients (20, 21). The recently published two-year results of the DILALA trial showed significantly less surgical interventions in patients treated with LL as compared to HP (14, 29). However, these results have to be interpreted with caution, as the increased re-operation rates in the patients who had HP is largely attributed to stoma reversal procedures. Additionally, during the second follow-up year, eight patients in the LL group developed recurrent diverticulitis compared with only two in the HP group. As shown in the present study, recurrence rates may occur well after 2 years. Due to the limited follow-up of most previous trials, complication and recurrence rates after LL are probably underestimated. Based on 12-month outcomes, LL was reported to be cost-effective in two studies (40, 41). However, considering that related interventions and readmissions could potentially occur after 12 months, the actual related costs of LL may be higher. Nevertheless, LL may result in the avoidance of a stoma and an uncomplicated follow-up in selected patients. Interestingly, in our cohort, 42% of patients had an ASA score of ≥ 3 , which correlated with a complicated outcome. Evidently, the present report is preliminary and should be interpreted with caution. Nevertheless, it appears that laparoscopic lavage predominantly results in morbidity and mortality in frail patients (*e.g.* those with high ASA-scores or multiple comorbidities). LL may be viable as the primary treatment option in a selected population. Therefore, accurate selection of patients that might benefit from this treatment is of importance to obtain satisfactory results, *e.g.* by taking age, immunosuppression, severe comorbidities (ASA ≥ 3), MPI and history of acute diverticulitis into consideration (26, 33). Long-term follow-up of other randomized controlled trials comparing LL to sigmoidectomy will provide more data on the efficacy and cost-effectiveness, as well as other studies assessing potential risk factors of treatment failure, and might help to improve accurate patient selection for LL.

Conclusion

In this retrospective cohort of 38 patients treated with LL for perforated diverticulitis, long-term recurrence, re-intervention, and readmission rates were high. Moreover, a complicated outcome was also present in patients who had initially been treated successfully with LL with relevant events occurring up to 6 years after initial surgery. Potentially, multiple comorbidities, high ASA scores, and short-term treatment failure of LL are of predictive value for an overall complicated outcome.

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Tables

Table 1 Baseline characteristics

No. of patients	38
Sex ratio (M:F)	24:14
Age (years)*	59 (45.5-68.3)
ASA score	
1-2	23
3-4	15
Co-morbidities	
None	20
1	6
2	6
> 2	6
Mannheim Peritonitis Index †	13.3 ± 5
Preoperative CRP (mmol/L) †	203 ± 143
Preoperative WBC count ($\times 10^3/\text{mm}^3$) †	15.4 ± 5.3
Preoperative hospital stay (days) †	
0	28
1	5
2	2
≥ 2	3
Free air	
No imaging	3
None	3
Pericolic	4
Distant	28
Operative findings	
Pelvic abscess, diffuse free air on CT (Hinchey II)	5
Localized cloudy or purulent exudate (Hinchey III)	29
Generalized cloudy or purulent exudate (Hinchey III)	4
Overt perforation	
Yes	2
No	36

ASA, American Society of Anesthesiologists; CRP, C-reactive protein; WBC, white blood cell; CT, computed tomography. Continuous values are *median (IQR) and †mean ± SD; discrete variables are absolute numbers.

Table 2 Overall outcomes

	Overall outcomes
No. of patients	38
Clinical follow-up (months)*	46 (7-77)
Study follow-up (months)*	90 (84-96)
Overall mortality	8 (21)
Total index admission time (days)*	14 (12-23)
ICU admission	6 (16)

Continuous variables are *median (IQR); discrete variables are absolute numbers (%).

Table 3 Recurrent diverticulitis, morbidity and surgical re-interventions

	< 90 days	≥ 90 days	Combined	Total events
Recurrent diverticulitis				
Sepsis not controlled/ongoing diverticulitis	7 (18)	0	7 (18)	7
Overall recurrence	1 (3)	11 (29)	12 (32)	17
1	1	8	9	9
≥ 2	0	3	3	8
Uncomplicated diverticulitis	1 (3)	5 (13)	6 (18)	10
Complicated diverticulitis	0	6 (16)	6 (18)	7
1	0	5	5	5
≥ 2	0	1	1	2
Time until first episode (days)		341 (115-795)		-
Morbidity				
Ileus	5 (13)	4 (11)	9 (24)	12
After laparoscopic lavage	5	1	6	6
After subsequent surgery	0	3	3	6
Intra-abdominal abscess	4 (11)	5 (13)	8 (23)	11
Enterocutaneous/ enterovaginal/ enterovesical/ ileosigmoid fistula	3 (8)	4 (11)	6 (18)	7
Midline incisional hernia	2 (5)	2 (5)	4 (11)	4
Burst abdomen	2 (5)	0	2 (5)	2
Parastomal hernia	0	2 (5)	2 (5)	2
Wound infection	2 (5)	1 (3)	3 (8)	3
Pneumonia	2 (5)	0	2 (5)	2
Pulmonary embolism	1 (3)	0	1 (3)	1
Atrial fibrillation	1 (3)	0	1 (3)	1
Surgical re-interventions				
Overall	6 (18)	10 (26)	12 (32)	29
1	4	4	2	2
≥ 2	2	6	10	10
≥ 1 emergency procedures	6 (100)	2 (20)	7 (58)	11
Sigmoid/anterior resection	3 (8)	6 (16)	9 (24)	9
Wedge excision sigmoid	0	1 (3)	1 (3)	1
Suture repair of perforated sigmoid	1 (3)	0	1 (3)	1
Stoma construction	3 (8)	6 (16)	9 (24)	9*
End colostomy	2	4	6	6
Loop Ileostomy	1	2	3	3
Stoma reversal	0	7	7	7
(Parastomal) hernia repair	0	3 (8)	3 (8)	3†
Relief of obstructive ileus	0	2 (5)	2 (5)	2
Abscess drainage (surgical)	1 (3)	0	1 (3)	2
Fistulotomy and abscess drainage	0	1 (3)	1 (3)	1
Repair of fascia dehiscence	2 (5)	0	2 (5)	2

Continuous variables are median (IQR); discrete variables are absolute numbers (%). Events that occurred multiple times are counted as one event per patient; the total events column depicts the cumulative number of events.

*One ileostomy and one colostomy were constructed in a separate procedure.

†One hernia repair procedure was performed simultaneously with a colostomy reversal.

Table 4 Readmissions

Readmissions	Overall outcomes	Total events
Any Readmission	15 (39)	50
1	4	4
≥ 2	11	46
Total readmission time (days)	11 (4-29)	346

Continuous variables are median (IQR); discrete variables are absolute numbers (%).

Table 5 Recurrence of diverticulitis and surgical re-interventions by time period

Time interval	0-1 year	0-3 years	0-5 years	End of follow-up
Recurrence of diverticulitis	8	13	16	17
Sigmoid/anterior resection	7	8	9	9
Reoperations	19	24	27	29

Table 6 Univariate analysis of baseline characteristics

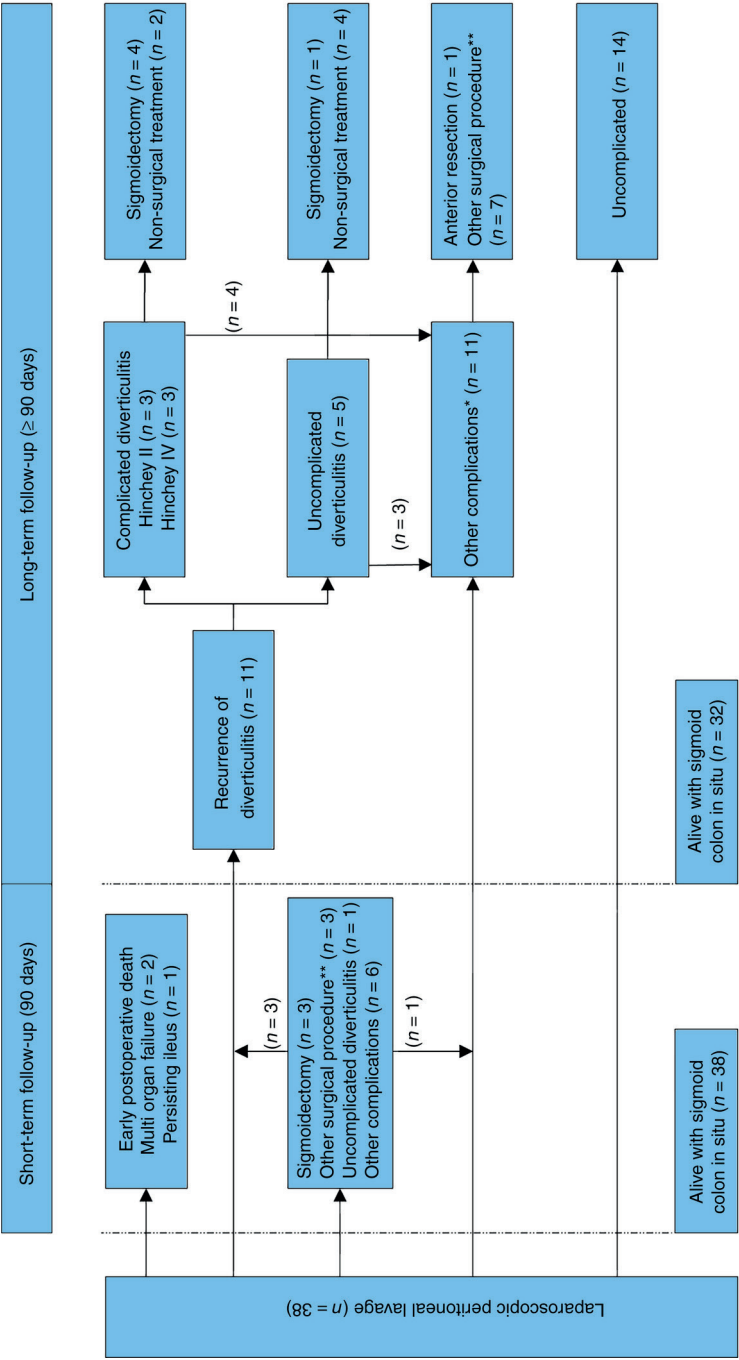
Variable	Uncomplicated Follow-up	Complicated Follow-up	P value
N	23	15	
Sex ratio (M : F)	15:8	9:6	1.00
Age	58 (44-68)	60 (46-70)	1.00*
ASA score			0.008
1-2	18	5	
3-4	5	10	
Co-morbidities			0.033
0 or 1	19	7	
≥ 2	4	8	
Mannheim Peritonitis Index*	11 (10-16)	15 (11-16)	0.184*
Preoperative CRP (mmol/L)*	172 (50-275)	242 (128.5-323)	0.068*
Preoperative white blood cell count (×103/mm3)*	16 (13.6-19.6)	13.4 (10.2-19.3)	0.374*
Preoperative hospital stay (days)			0.630
0 or 1	19	14	
≥ 2	4	1	
Free air			0.545
No	1	2	
Pericolic	3	1	
Distant	16	12	
Per operative diagnosis			0.504
Pelvic abscess, diffuse free air on CT (Hinchey II)	2	3	
Localized cloudy or purulent exudate (Hinchey III)	19	10	
Generalized cloudy or purulent exudate (Hinchey III)	2	2	
Overt perforation	1	1	1.00
Primary treatment failure	0	7	0.001

Continuous values are median (IQR); discrete variables are absolute numbers. ASA, American Society of Anesthesiologists; CRP, C-reactive protein; CT, computed tomography.

*Mann-Whitney U test.

Figures

Figure 1 Flowchart of clinical outcomes.



Non-surgical treatment comprises all medical interventions not requiring general anesthesia including radiological interventions (e.g.: intravenous antibiotics and fluid therapy or endoscopic dilatation). *Other complications comprise: ileus, intraabdominal abscesses, fistulas, multi-organ failure, incisional hernias, and parastomal hernias. **Other surgical procedures comprise: stoma construction, stoma reversal, (parastomal) hernia repair, relieve of obstructive ileus, repair of fascial dehiscence, repair of sigmoid perforation, fistulotomy, abscess drainage, wedge resection of the sigmoid. The number of patients that had multiple events is indicated in brackets next to arrows.

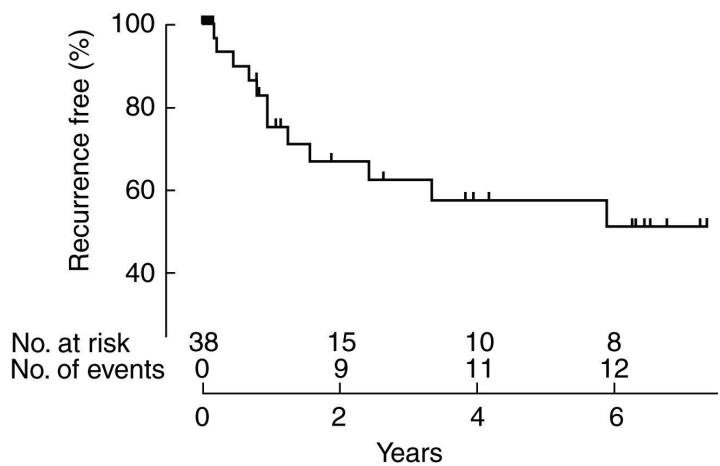


Figure 2 Recurrence-free survival

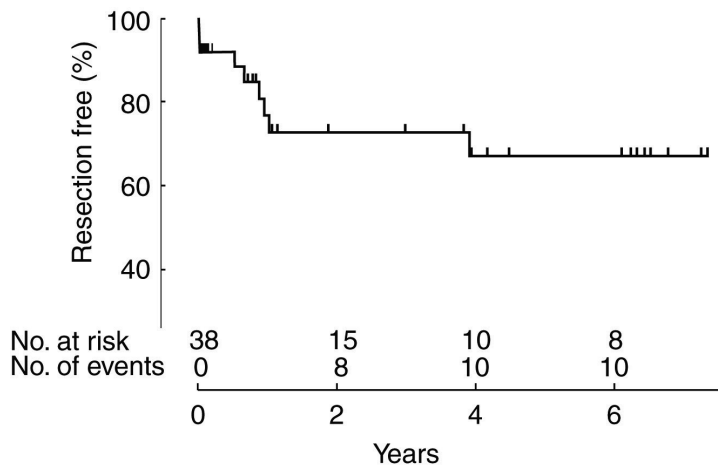
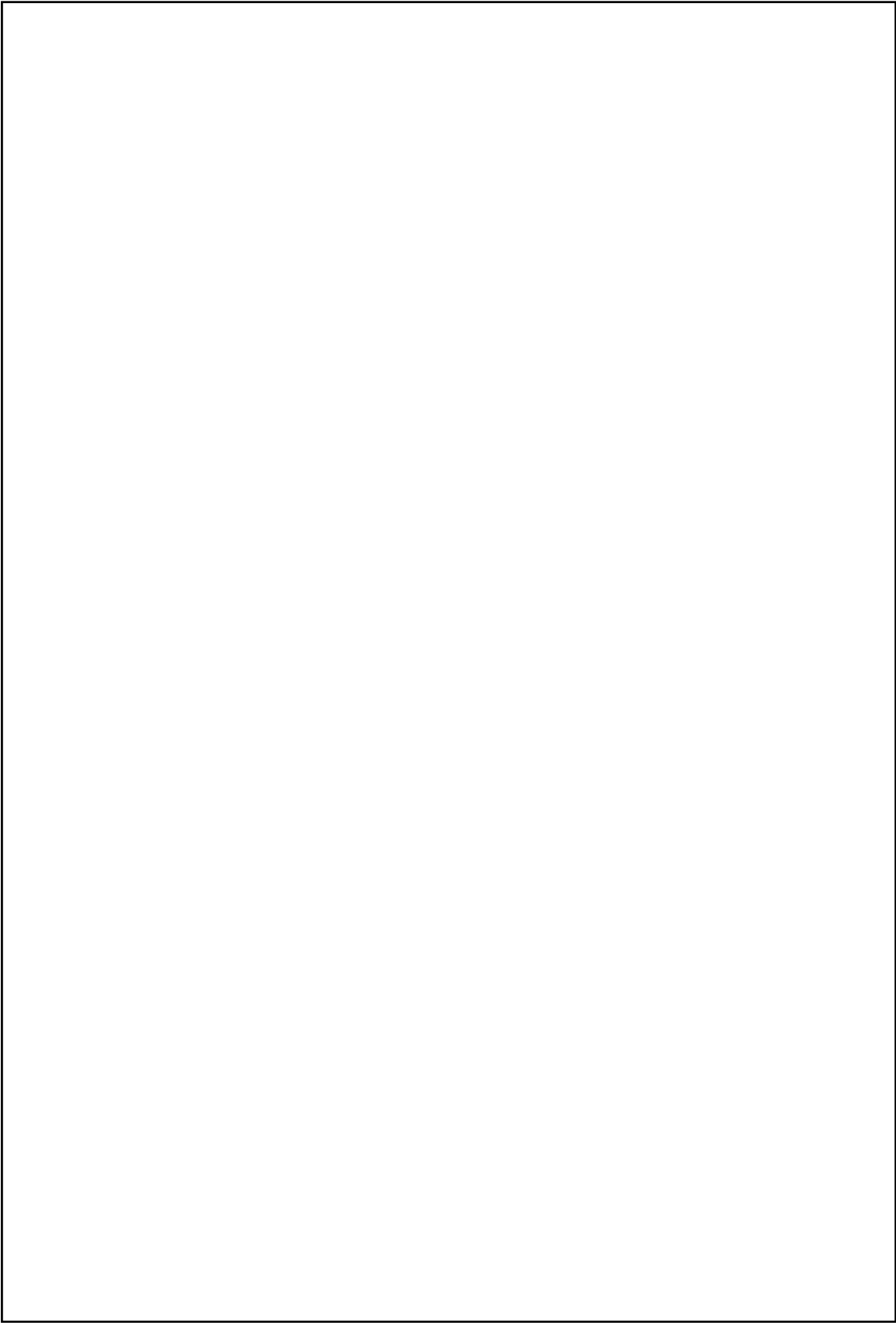


Figure 3 Resection-free survival

The first part of the paper discusses the importance of understanding the cultural context of the research. It highlights the need for researchers to be sensitive to the values and beliefs of the communities they are studying. This is particularly important in the field of education, where cultural differences can significantly impact learning outcomes. The paper then moves on to discuss the challenges of conducting research in culturally diverse settings. It notes that researchers often face difficulties in establishing rapport with participants and in interpreting their responses. To address these challenges, the paper suggests several strategies, including the use of local informants and the development of culturally appropriate research instruments. The final part of the paper discusses the importance of ethical considerations in cross-cultural research. It emphasizes the need for researchers to obtain informed consent from participants and to ensure that their research does not cause harm or exploitation. The paper concludes by noting that while cross-cultural research is a complex and challenging endeavor, it is also a highly rewarding one that can lead to a deeper understanding of the world and its diverse cultures.

Part II

Resectional treatment of
complicated diverticulitis



Chapter 5

Hartmann's procedure versus sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (LADIES): a multicentre, parallel-group, randomised, open-label, superiority trial

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Summary

Background

Previous studies have suggested that sigmoidectomy with primary anastomosis is superior to Hartmann's procedure. The likelihood of stoma reversal after primary anastomosis has been reported to be higher and reversal seems to be associated with lower morbidity and mortality. Although promising, results from these previous studies remain uncertain because of potential selection bias. Therefore, this study aimed to assess outcomes after Hartmann's procedure versus sigmoidectomy with primary anastomosis, with or without defunctioning ileostomy, for perforated diverticulitis with purulent or faecal peritonitis (Hinchey III or IV disease) in a randomised trial.

Methods

A multicentre, randomised, open-label, superiority trial was done in eight academic hospitals and 34 teaching hospitals in Belgium, Italy, and the Netherlands. Patients aged between 18 and 85 years who presented with clinical signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion if plain abdominal radiography or CT scan showed diffuse free air or fluid. Patients with Hinchey I or II diverticulitis were not eligible for inclusion. Patients were allocated (1:1) to Hartmann's procedure or sigmoidectomy with primary anastomosis, with or without defunctioning ileostomy. Patients were enrolled by the surgeon or surgical resident involved, and secure online randomisation software was used in the operating room or by the trial coordinator on the phone. Random and concealed block sizes of two, four, or six were used, and randomisation was stratified by age (<60 and ≥60 years). The primary endpoint was 12-month stoma-free survival. Patients were analysed according to a modified intention-to-treat principle. The trial is registered with the Netherlands Trial Register, number NTR2037, and ClinicalTrials.gov, number NCT01317485.

Findings

Between July 1, 2010, and Feb 22, 2013, and June 9, 2013, and trial termination on June 3, 2016, 133 patients (93 with Hinchey III disease and 40 with Hinchey IV disease) were randomly assigned to Hartmann's procedure (68 patients) or primary anastomosis (65 patients). Two patients in the Hartmann's group were excluded, as was one in the primary anastomosis group; the modified intention-to-treat population therefore consisted of 66 patients in the Hartmann's procedure group (46 with Hinchey III disease, 20 with Hinchey IV disease) and 64 in the primary anastomosis group (46 with Hinchey III disease, 18 with Hinchey IV disease). In 17 (27%) of 64 patients assigned to primary anastomosis, no stoma was constructed. 12-month stoma-free survival was significantly better for patients undergoing primary anastomosis compared with Hartmann's procedure (94.6% [95% CI 88.7–100] vs 71.7% [95% CI 60.1–83.3], hazard ratio 2.79 [95% CI 1.86–4.18]; log-rank $p < 0.0001$). There were no significant differences in short-term morbidity and mortality after the index procedure for Hartmann's procedure compared with primary anastomosis (morbidity: 29 [44%] of 66 patients vs 25 [39%] of 64, $p = 0.60$; mortality: two [3%] vs four [6%], $p = 0.44$).

Interpretation

In haemodynamically stable, immunocompetent patients younger than 85 years, primary anastomosis is preferable to Hartmann's procedure as a treatment for perforated diverticulitis (Hinchey III or Hinchey IV disease).

Funding

Netherlands Organisation for Health Research and Development.

Introduction

Diverticular disease is the third most costly gastrointestinal disorder in developed countries, making it an important condition in terms of health-care utilisation (1). An estimated 8–35% of patients with acute diverticulitis present with complicated disease, including abscess formation (Hinchey classification Ib and II) or perforation with purulent or faecal peritonitis (Hinchey III or IV) (2, 3).

In cases of perforated diverticulitis with purulent or faecal peritonitis, emergency operative treatment is standard practice (4–7). Hartmann's procedure - resection with end colostomy construction - remains the favoured option for most surgeons and avoids the risk of anastomotic leakage (3, 8). However, several studies have suggested that sigmoidectomy with primary anastomosis is equal to Hartmann's procedure in terms of post-operative mortality and morbidity (5, 7, 9). Additionally, the likelihood of reversal of end colostomies after Hartmann's procedure has been reported to be lower (50–60%) than that of closure of defunctioning ileostomies after sigmoidectomy with primary anastomosis (85%), thereby increasing associated health-care costs and negatively affecting quality of life (10–12). Moreover, Hartmann's procedure reversal is associated with high mortality and morbidity (13, 14), whereas primary anastomosis allows for a safer, less challenging closure procedure (12, 13, 15). In selected cases of sigmoidectomy with primary anastomosis, a defunctioning ileostomy might even be avoided (8, 16).

Despite increased interest in sigmoidectomy with primary anastomosis and its potential advantages, high-quality evidence from randomised studies comparing this procedure with Hartmann's procedure is scarce, particularly with regard to stoma-free survival, which, as a single outcome measure, reflects both the risk of mortality and the likelihood of stoma reversal. Therefore, the aim of the DIVA arm of the international, multicentre, randomised controlled LADIES trial (17), was to compare Hartmann's procedure with primary anastomosis (with or without defunctioning ileostomy) to determine the optimal strategy for perforated diverticulitis with purulent or faecal peritonitis.

Methods

Study design and participants

The LADIES trial (18) was a multicentre, randomised, open-label, superiority trial done at 34 teaching hospitals and eight academic hospitals in Belgium, Italy, and the Netherlands. Initially, the trial had a combined design to compare laparoscopic peritoneal lavage with sigmoidectomy for purulent perforated diverticulitis (LOLA arm) and Hartmann's procedure with sigmoidectomy with primary anastomosis in both purulent and faecal perforated diverticulitis (DIVA arm) (18). After preliminary termination of the LOLA arm, patients with purulent peritonitis were no longer randomly assigned to laparoscopic lavage and enrolment of patients with both purulent or faecal peritonitis continued in the DIVA arm (19).

Patients aged between 18 and 85 years, who presented with clinical signs of general peritonitis and suspected perforated diverticulitis were eligible for inclusion if plain abdominal radiography or CT scan showed diffuse free air or fluid. Patients with Hinchey I and II diverticulitis were not eligible for inclusion. Details of the Hinchey classification are provided in the appendix (Table 1)(20). Exclusion criteria were dementia, previous sigmoidectomy, previous pelvic radiotherapy, chronic steroid treatment (≥ 20 mg daily), and preoperative shock requiring inotropic support. Before the study procedure, written informed consent was obtained from patients by the surgeon or surgical resident involved.

The study was designed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and received ethics approval from the institutional review board (IRB) of the University Medical Centre Amsterdam and local approval was provided in the participating hospitals.

Randomisation and masking

Patients underwent diagnostic laparoscopy to confirm their diagnosis, exclude other causes of peritonitis, and distinguish between types of peritonitis. After confirmation of diagnosis, patients with purulent peritonitis (Hinchey III) were randomly assigned (2:1:1) within the LOLA arm between laparoscopic lavage, Hartmann's procedure, or sigmoidectomy with primary anastomosis with or without defunctioning ileostomy. Patients with faecal peritonitis or an overt perforation (Hinchey IV) were randomly assigned within the DIVA arm. In the DIVA arm, patients were allocated (1:1) to Hartmann's procedure or primary anastomosis, with or without defunctioning ileostomy. After termination of the LOLA arm, random assignment to Hartmann's procedure and sigmoidectomy with primary anastomosis (1:1) continued to allow further comparison between these strategies. Patients with purulent peritonitis who underwent Hartmann's procedure or sigmoidectomy with primary anastomosis in the LOLA arm before its termination were included in the present analyses.

Patients were enrolled by the surgeon or surgical resident involved. Secure online randomisation software (ALEA version 2.2) was used in the operating room or by the trial coordinator on the phone. Random concealed block sizes of two, four, or six were generated by the randomisation software and used for randomisation. Randomisation was stratified by age (<60 years vs ≥ 60 years). Patients, physicians, and researchers were not masked to the allocated treatment during the complete study period after randomisation.

Procedures

The surgical procedures have previously been described in detail (18). When allocated to Hartmann's procedure, resection of the diseased segment was done without the explicit requirement of the distal transection line to be on the proximal rectum. Construction of an end colostomy and closure of the rectal stump were done according to the preference of the operating surgeon. For sigmoidectomy with primary anastomosis, the distal transection margin was on the proximal rectum and the proximal margin was determined by the absence of wall thickening due to diverticulitis. Anastomotic construction and configuration were done according to the surgeon's preference. Decisions on type of anastomosis, minimally invasive surgery, construction of defunctioning ileostomy, and drain placement were left at the surgeon's discretion. Stoma reversal was offered to patients if they were willing to undergo surgery and if they were considered operable by the surgeon and anaesthesiologist.

After the index procedure, patients were followed up at least once in an outpatient setting and follow-up after stoma reversal was done according to local protocols. Patients who were not in active follow-up at 12 months were contacted to verify remaining follow-up.

We measured health-related quality of life with EuroQol-5D-3-level, Short Form-36 v2, and gastrointestinal quality-of-life index (21), at weeks 2 and 4, and months 3, 6, and 12 of follow-up.

An electronic case report form was used to collect data on patient demographics, including sex, age, body-mass index, medical history, medication, American Society of Anesthesiologists (ASA) score, physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM), acute physiology and chronic health evaluation (APACHE) II score, Mannheim peritonitis index (MPI), and operative and postoperative characteristics, such as surgical approach, type of anastomosis, operating time, intra-operative blood loss, and duration of hospital stay. Moreover, during 12-month follow-up, outcomes such as major and minor morbidity, mortality, surgical reinterventions, readmissions to hospital, stoma reversal procedures, incisional hernia occurrence, and the number of days alive and outside of hospital were recorded. Questionnaires were sent by mail and the trial coordinator contacted patients who did not return or fill out questionnaires. During the study period until July 31, 2014, a chart review was done in 28 Dutch participating centres that included at least one patient in the trial to assess baseline characteristics of eligible non-included patients (19).

Outcomes

The primary endpoint was 12-month stoma-free survival. Secondary endpoints were short-term mortality and morbidity, regarded as separate endpoints, after index and reversal procedures, operative (presence of gastrointestinal surgeon, laparoscopic procedure, operating time, drain placement, and anastomotic construction and configuration) and postoperative (type of postoperative admission, length of postoperative stay, intensive care unit stay, and days until normal intake) care characteristics, and health-related quality of life. We defined short-term as within 30 days after surgery or until discharge, if the patient remained in hospital at that time. Predefined major morbidity included any of the following events or conditions: surgical reintervention, percutaneous abscess drainage, fascial dehiscence, urosepsis, myocardial infarction, renal failure, and respiratory insufficiency. Other prespecified secondary outcomes were duration of hospital stay, incisional hernia occurrence, and the number of days alive and outside of the hospital.

Separately, complications were scored according to the Clavien-Dindo classification (22) over a 90-day period. Elective stoma reversal was not defined as morbidity or reintervention in either treatment group. Although prespecified as a secondary endpoint, an economic evaluation of health-care use and associated costs was not included in the present study, but will be reported separately.

Statistical analysis

We suspected postoperative mortality to be 15% for both treatment strategies (7). Around 60% of patients in the Hartmann's procedure group and 85% of patients in the sigmoidectomy with primary anastomosis group were estimated to undergo stoma reversal (13, 14). When corrected for expected mortality, reversal rates were calculated to be 50% and 72%, respectively. Before termination of the LOLA arm, a sample size of 264 was needed, which was based on an expected difference of 15% (10% vs 25%) in combined mortality and major morbidity between laparoscopic lavage and sigmoidectomy, respectively (90% power; 5% two-sided α). After termination of the LOLA arm, a sample size calculation was done based on the primary endpoint of the DIVA arm. We calculated a sample size of 212 patients would be needed to show a significant difference in 12-month stoma-free survival with log-rank statistics with 90% power and a two-sided α of 5%, based on an estimated difference of 22% (50% vs 72% for Hartmann's procedure and primary anastomosis, respectively). When corrected for potential loss to follow-up (10%), the sample size was 236 patients.

Patients were analysed according to a modified intention-to-treat principle, as three patients were excluded shortly after randomisation because of the following alternate diagnoses: wedge excision of giant diverticulum in the absence of other diverticula (one patient in the primary anastomosis group with Hinchey IV disease), subtotal colectomy with end ileostomy for colonic metastases of a previously unknown pancreatic carcinoma (one patient in the Hartmann's procedure group with Hinchey III disease), and rectosigmoid cancer in the absence of diverticula (one patient in the Hartmann's procedure group with Hinchey IV disease). We estimated 12-month stoma-free survival with the Kaplan-Meier method and analysed differences in survival with

the Mantel-Cox log-rank test, without adjustment for other covariates. We used a post-hoc Cox regression analysis, with treatment and age stratification groups as covariates, to adjust for age stratification. We compared categorical data with Fisher's exact test and reported the results as numbers with percentages. Depending on normality, we tested continuous variables with Student's t test or Mann-Whitney U test and presented the results as means with SD or medians with IQR. We analysed questionnaires according to the relevant guidelines and presented results as subscales and summarised scores. For questionnaires, we imputed missing data with a regression model with predictive mean matching, creating ten imputed data sets by taking treatment group, Hinchey grade, and questionnaire values of other time points into account. We calculated pooled means if at least one questionnaire was returned and corrected p values for multiple testing with the Benjamini-Hochberg method.

A data safety monitoring board, comprising independent clinical, epidemiological, and statistical experts, was established to assess trial progress and safety. The IRB approved a formal charter, allowing the data safety monitoring board to stop the study for safety reasons or early treatment superiority outside any prespecified definitions. After inclusion of every 25 patients, safety variables were supplied to the data safety monitoring board by the trial coordinator. In cases of patients with study-related severe morbidity or mortality, the data safety monitoring board was granted access to these individual data.

Statistical analyses were done with SPSS version 24.0 and R version 3.4.1. The trial is registered with the Netherlands Trial Register, number NTR2037, and ClinicalTrials.gov, number NCT01317485.

Role of the funding source

The LADIES trial was investigator-initiated and supported by a grant from the Netherlands Organisation for Health Research and Development. The funder of the study critically reviewed and adjusted the study design, but had no role in data collection, data analysis, data interpretation, writing of the report, or the submission process. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July 1, 2010, and Feb 22, 2013, 90 patients (47 assigned to laparoscopic lavage and 43 to sigmoidectomy) were recruited and enrolled in the trial, after which recruitment was temporarily stopped, as advised by the data safety monitoring board, because of safety concerns in the LOLA arm at the third interim analysis. After IRB approval, randomisation (1:1) between Hartmann's procedure and sigmoidectomy with primary anastomosis continued in the DIVA arm, as safety concerns were limited to the laparoscopic lavage group (19). Continuation of the study commenced on June 9, 2013, and lasted until June 3, 2016, after which the DIVA arm was prematurely terminated because of slow patient accrual, leading to substantial delays in trial progression. After both the data safety monitoring board and IRB approved early termination, 12-month follow-up was continued and finished for all 130 included patients. Included patients were from one Belgian hospital, two Italian hospitals, and 25 Dutch hospitals (19 teaching and six academic hospitals).

133 patients (93 with Hinchey III disease and 40 with Hinchey IV disease) were randomly assigned to Hartmann's procedure or sigmoidectomy with primary anastomosis (Hinchey III: 47 patients to Hartmann's procedure and 46 patients to primary anastomosis; Hinchey IV: 21 patients to Hartmann's procedure and 19 patients to primary anastomosis; Figure 1). Of the patients with Hinchey III disease, one patient in the primary anastomosis group crossed over to laparoscopic lavage and five patients crossed over to Hartmann's procedure. One patient assigned to Hartmann's procedure was excluded because of sigmoid carcinoma (metastases of previously undiagnosed pancreatic carcinoma; this patient underwent subtotal colectomy with end ileostomy for colonic metastases) and one patient crossed over to primary anastomosis. Of the patients with Hinchey IV disease, one patient assigned to Hartmann's procedure was excluded because of rectosigmoid carcinoma (Figure 1). Two patients assigned to primary anastomosis crossed over to Hartmann's procedure and one was excluded because of a giant sigmoid diverticulum requiring wedge excision. Reasons for crossover are listed in the appendix (Table 2).

Thus, 130 patients were included in the modified intention-to-treat population: 66 patients in the Hartmann's procedure group and 64 in the primary anastomosis group; 92 patients had Hinchey III disease and 38 had Hinchey IV disease (Figure 1). 82 patients were included in the analysis of stoma reversal, and in the remaining patients no stoma was constructed (18 patients) or no reversal was done during follow-up (29 patients). One patient was lost to follow-up after short-term follow-up and could therefore only be included in analyses of short-term outcomes after the index procedure. The number of patients included per centre is provided in the appendix (Table 3).

We observed no major differences between randomised groups in terms of baseline characteristics in the modified intention-to-treat population (Table 1). In the Hartmann's procedure group, 20 (30%) of 66 patients had Hinchey grade IV diverticulitis and in the primary anastomosis group, 18 (28%) of 64 patients had Hinchey grade IV diverticulitis. A gastrointestinal surgeon was present during the procedure for 57 (86%)

of 66 patients in the Hartmann's procedure group and 58 (91%) of 64 patients in the primary anastomosis group. Procedures were done laparoscopically in 20 (30%) of 66 patients in the Hartmann's procedure group and 17 (27%) of 64 patients in the primary anastomosis group. None of these surgeries were converted to an open procedure. A comparison between baseline characteristics of patients with Hinchey III and Hinchey IV disease and data for separate Hinchey grades are provided in the appendix (Tables 4-5). We also compared baseline patient and perioperative characteristics and outcomes between eligible non-included patients (235 patients) and included patients (appendix Table 6). We observed significantly lower preoperative disease severity scores in non-included patients compared with included patients (eg, median Portsmouth-POSSUM predicted mortality 4.4% [IQR 2.8–11.6] vs 6.1% [4.3–11.3]; $p=0.011$; and median POSSUM predicted morbidity scores 64.8% [IQR 52.5–82.4] vs 71.7% [61.2–82.3]; $p=0.0028$), whereas ASA, APACHE II, and MPI scores were not significantly different between non-included and included patients. 20 (9%) of 235 eligible non-included patients died, compared with six (5%) of 130 patients in the study population ($p=0.21$). In the non-included patients, the presence of a gastrointestinal surgeon was significantly less likely compared with the included patients (68.7% vs 88.5%; $p<0.0001$).

Patients in the primary anastomosis group had significantly better 12-month stoma-free survival compared with patients in the Hartmann's procedure group (94.6% [95% CI 88.7–100] vs 71.7% [95% CI 60.1–83.3], hazard ratio [HR] 2.79 [95% CI 1.86–4.18]; log-rank $p<0.0001$; Figure 2). Median time to being stoma-free was 101.0 days (95% CI 71.5–130.5) for patients in the primary anastomosis group and 186.0 days (138.0–234.0) for patients in the Hartmann's procedure group. A post-hoc subgroup analysis found a HR for stoma-free survival of 2.35 (95% CI 1.33–4.15; log-rank $p=0.0032$) for patients younger than 60 years versus 3.41 (1.88–6.20; log-rank $p<0.0001$) for patients aged 60 years and older. Moreover, when adjusted for age (<60 years or ≥ 60 years), the HR for stoma-free survival was 2.72 (95% CI 1.81–4.08). Survival curves for the primary outcome in both separate Hinchey groups are given in the appendix (Figures 2-3). In both Hinchey groups, patients in the primary anastomosis group had significantly better 12-month stoma-free survival (Hinchey III: primary anastomosis 95.3% [95% CI 89.7–100.0] vs Hartmann's procedure 79.8% [67.5–92.2], HR 2.35 [95% CI 1.49–3.71]; log-rank $p=0.00025$; Hinchey IV: primary anastomosis 92.2% [CI 77.7–100] vs Hartmann's procedure 51.9% [28.2–75.6], HR 4.15 [1.71–10.1]; log-rank $p=0.0016$).

We found no significant differences in short-term postoperative outcomes of the index procedures (Table 2, Table 3). 29 (44%) of 66 patients in the Hartmann's procedure group and 25 (39%) of 64 patients in the primary anastomosis group had major or minor morbidity; major morbidity was noted in eight (12%) of 66 patients in the Hartmann's procedure group and nine (14%) of 64 patients in the primary anastomosis group (Table 2). In the Hartmann's procedure group, two (3%) patients with Hinchey IV disease died from ongoing sepsis with multiorgan failure. In the primary anastomosis group, four (6%) patients died: three patients with Hinchey IV disease because of ongoing sepsis and one patient with Hinchey III disease, with known cardiovascular comorbidities, of sepsis further complicated by an occlusion of the right common iliac artery. One of

these four patients assigned to primary anastomosis crossed over to the Hartmann's procedure group. Mortality was not significantly different between patients assigned to Hartmann's procedure versus primary anastomosis ($p=0.44$). Surgical reinterventions in the Hartmann's procedure group consisted of revision of necrotic stoma (two patients), closure after open abdomen treatment (one patient), and relaparotomy for ongoing sepsis (one patient). In the primary anastomosis group, surgical reinterventions were repair of fascial dehiscence (one patient), surgical abscess drainage (one patient), and relaparotomy for ongoing sepsis (two patients). One of the patients who underwent relaparotomy for ongoing sepsis required a second relaparotomy.

90-day Clavien-Dindo scores showed no significant differences between the groups, with grade IIIb or worse complications in 12 (18%) of 66 patients in the Hartmann's procedure group and nine (14%) of 63 patients in the primary anastomosis group (appendix Table 7). Overall morbidity was not significantly different for Hartmann's procedure and primary anastomosis in patients with Hinchey III (17 [37%] of 46 patients in the Hartmann's procedure group vs 17 [37%] of 46 patients in the primary anastomosis group, $p=1.0$) and Hinchey IV (12 [60%] of 20 patients in the Hartmann's procedure vs eight [44%] of 18 patients in the primary anastomosis group; $p=0.52$) disease (appendix Table 8).

In the Hartmann's procedure group, a stoma was constructed in 65 (98%) of 66 patients, whereas only 46 (73%) of 64 patients in the primary anastomosis group had a stoma constructed (Table 4). In the patients in the primary anastomosis group without a stoma, major and minor morbidity were both 12% (two of 17 patients), overall morbidity was 24% (four of 17 patients), and there were no deaths related to the index procedure. A comparison between patients in the primary anastomosis group with and without an ileostomy is given in the appendix (Table 9). In all but two patients, postoperative histopathology details were available, which showed a sigmoid carcinoma in two patients (one patient with Hinchey III diverticulitis and one with Hinchey IV diverticulitis).

44 (68%) of 65 patients with a stoma in the Hartmann's procedure group underwent stoma reversal, compared with 38 (83%) of 46 patients with a stoma in the primary anastomosis group ($p=0.085$; Table 4). Hartmann's procedure reversal was done laparoscopically in 20 (45%) of 44 patients. In 16 (25%) of 66 patients allocated to Hartmann's procedure and one crossover patient from the primary anastomosis group, both the index procedure and Hartmann's reversal procedure were done laparoscopically and without conversion.

For postoperative outcomes of stoma reversal, overall morbidity was significantly lower in the primary anastomosis group compared with the Hartmann's procedure group (13 [30%] of 66 patients vs three [8%] of 38 patients; $p=0.023$; Table 5). Furthermore, the median interval to reversal (113.5 days [IQR 80.0–155.0] vs 133.0 days [102.0–208.0]; $p=0.021$) and median postoperative stay (4.0 days [IQR 2.8–5.0] vs 5.0 days [4.0–6.0]; $p=0.011$) were significantly shorter for the primary anastomosis group. There were no deaths related to stoma reversal. One patient in the Hartmann's procedure group had an anastomotic leakage after stoma reversal, for which an end colostomy was constructed.

For patients with Hinchey IV diverticulitis, there was no overall morbidity related to stoma reversal in the primary anastomosis group, compared with 30% (three of ten patients) in the Hartmann's procedure group ($p=0.21$; appendix Table 10). Overall, no stoma reversal was done in 29 patients (appendix Table 11). 19 patients were alive with a stoma at 12-month follow-up, of whom six patients (all in the Hartmann's procedure group) eventually underwent stoma reversal outside the follow-up period after a median total duration of 13.2 months (IQR 12.7–23.3).

Although not significantly different, overall morbidity for both the index procedure and any subsequent reversal was lower for primary anastomosis than for Hartmann's procedure (25 [40%] of 63 patients vs 37 [56%] of 66 patients; $p=0.078$; Table 6). Furthermore, although not significantly different, the overall median postoperative stay was shorter for primary anastomosis than for Hartmann's procedure (12.5 days [IQR 9.0–16.8] vs 14.0 days [10.8–19.0]; $p=0.054$). Overall, two (3%) of 66 patients in the Hartmann's group and four (6%) of 63 patients in the primary anastomosis group died. Overall, no postoperative urosepsis occurred. The median number of days alive and outside of the hospital was 348.0 (IQR 335.5–354.0) for Hartmann's procedure and 351.0 (342.3–358.0) for primary anastomosis ($p=0.21$). A midline incisional hernia was diagnosed in eight patients (five in the Hartmann's procedure group and three in the primary anastomosis group), of which four were treated conservatively, whereas the remaining four underwent open repair (two patients), laparoscopic repair (one patient), or repair during Hartmann's reversal (one patient). In two of these patients no stoma was constructed, in three the stoma was reversed before hernia occurrence, and in the remaining three the stoma was reversed after hernia occurrence. One patient with a midline incisional hernia also had a parastomal hernia without undergoing stoma reversal during follow-up. Ten patients in the Hartmann's procedure group developed a parastomal hernia during follow-up, of which three were treated conservatively, and the remaining seven underwent Hartmann's procedure reversal. After stoma reversal, stoma site incisional hernia was diagnosed in three patients (two in the Hartmann's procedure group and one in the primary anastomosis group). Moreover, one patient in the primary anastomosis group developed a trocar site hernia.

Quality-of-life results and questionnaire response rates are given in the appendix (Tables 12–13). After correction for multiple testing, no significant differences between the groups were found in any of the subscales and summarised scores.

Discussion

This randomised trial, comparing Hartmann's procedure to sigmoidectomy with primary anastomosis in patients with perforated diverticulitis and purulent or faecal peritonitis, showed significantly better 12-month stoma-free survival for patients in the primary anastomosis group, without significant differences in short-term morbidity and mortality. Furthermore, we found significantly lower short-term overall morbidity after stoma reversal for primary anastomosis, and a significantly shorter median time to reversal and postoperative stay after reversal.

Other randomised clinical trials comparing Hartmann's procedure with primary anastomosis have shown similar outcomes regarding the difference in morbidity after the index and reversal procedures. In a study by Oberkofler and colleagues (23), which compared 30 patients who underwent Hartmann's procedure with 32 patients who underwent primary anastomosis (with defunctioning ileostomy), no difference was found in the number of overall complications. Similarly, a trial by Binda and colleagues (24), did not find a difference in morbidity between Hartmann's procedure and primary anastomosis. Bridoux and colleagues (25) also reported similar overall morbidity rates for Hartmann's procedure and primary anastomosis. With the exception of a significant difference in overall morbidity after the stoma reversal procedure in favour of primary anastomosis, short-term outcomes after the index procedure were also similar in our study. Exact morbidity figures differ between studies, which might be due to a difference in definitions of morbidity. Although no significant differences were found in morbidity rates after the index procedure and both procedures combined in the present trial, the absolute number of events in each group was higher in the Hartmann's procedure group than in the primary anastomosis group. Furthermore, mortality was twice as high after primary anastomosis than with Hartmann's procedure, although the absolute difference was low (four patients in the primary anastomosis group vs two patients in the Hartmann's procedure group). One of the four deceased patients in the primary anastomosis group crossed over to Hartmann's procedure. When interpreting these results, it should be noted that the study was not powered to detect clinically significant differences in these secondary outcomes.

To our knowledge, this is the first trial to report on 12-month stoma-free survival. Our trial showed significantly better stoma-free survival for patients undergoing primary anastomosis compared with patients undergoing Hartmann's procedure. This difference might be explained by the higher percentage of stoma reversals and the higher number of patients without a stoma in the primary anastomosis group, since the decision to construct a defunctioning ileostomy was left to the discretion of the surgeon. These results reflect the important benefit of potentially avoiding stoma construction in patients undergoing primary anastomosis, which is not possible in patients undergoing Hartmann's procedure. Moreover, the significantly lower percentage of post-reversal overall morbidity associated with primary anastomosis, as well as the shorter interval until stoma reversal and postoperative stay after stoma reversal, further advocate the benefits of primary anastomosis. Results from a recent meta-analysis of experimental and observational studies (26) indicate decreased morbidity rates after stoma reversal

for primary anastomosis, whereas in a meta-analysis of three randomised studies (27), Hartmann's procedure and primary anastomosis were not found to be different in terms of mortality or overall morbidity. Additionally, no difference in the number of permanent stoma was reported between the groups, despite the fact that two of three studies reported more stoma reversals after primary anastomosis than after Hartmann's procedure (23, 25, 27).

Overall, baseline patient characteristics did not differ significantly between patients with Hinchey III and Hinchey IV diverticulitis. Additionally, the primary endpoint was found to be significantly better for patients undergoing primary anastomosis in both of these Hinchey grades. Moreover, from these analyses, morbidity and mortality in those with Hinchey IV disease appeared to be higher than for those with Hinchey III disease. Nevertheless, differences in secondary outcomes between Hartmann's procedure and primary anastomosis in patients with Hinchey IV diverticulitis were not clearly shown in our study, although these results should be interpreted with caution because of the relatively small group size.

An important limitation of this trial is its premature termination and consequent non-achievement of the planned sample size because of low accrual rates. Trials done in an emergency care setting are vulnerable to premature discontinuation because of slow patient recruitment (28). Moreover, surgical trials with invasive interventions tend to be more frequently discontinued because of slow recruitment (29). In patients with suspected perforated diverticulitis, the narrow time window in which decisions regarding trial participation had to be made by both patients and surgeons might have been an important limitation. Moreover, because of the emergency setting of our trial and the large number of participating hospitals, awareness among clinicians of the trial might not always have been optimal, despite efforts to increase this. Furthermore, treatment preferences of involved surgeons and subsequent refusal to randomly assign patients might have affected patient inclusion. Similar difficulties with slow patient recruitment and underlying reasons for these difficulties have been reported in three previously published trials (23-25). Early termination of trials for reasons of benefit potentially leads to overestimation of treatment effects (30). However, in the case of our study, termination was because of slow accrual, in which case the main concern is loss of study power. However, our primary endpoint was still statistically significant, which could partly be explained by the fact that the sample size calculation was based on 90% power (31).

Selection bias might have been introduced before randomisation due to surgeon or patient preferences. As a complete account of patients excluded before study enrolment could not be obtained in this trial, we cannot completely rule out the influence of selection bias. However, data on 235 non-included patients were available through an extensive medical chart review in many participating hospitals. Therefore, by contrast with previous trials, an important strength of the present study was the possibility to compare baseline characteristics of eligible non-included patients with included patients to assess potential selection bias and increase external validity (32). These results showed that included patients had slightly worse preoperative disease severity, although absolute

differences were small. The proportion of procedures for which a gastrointestinal surgeon was present was significantly lower in non-included patients than in included patients. Although speculative, this fact could be explained by increased trial awareness of the involved gastrointestinal surgeons and more willingness to enroll patients, leading to a higher percentage of patients operated on by gastrointestinal surgeons. A population-based cohort study (33) found 24.3% mortality in a cohort with a mean age of 72 years (range 30–95), both of which are higher values than in our study. Additionally, Gawlick and Nirula (34) reported mortality rates of 6.2% and 7.9% and mean ages of 63.4 years (SD 15.8) and 63.0 years (15.0) for primary anastomosis and Hartmann's procedure, respectively. These figures are more in line with the present study, as well as with the cumulative mortality in previously published trials (six [5.2%] of 116 patients for primary anastomosis) and 12 [8.7%] of 138 patients for Hartmann's procedure) (27). Importantly, we did not find large differences in the mortality of included and non-included patients in the present study. Additionally, another strength of our trial is the multicentre setting, which increases the generalisability of the results and has made it possible to analyse, to our knowledge, the largest cohort of patients randomly assigned to Hartmann's procedure or primary anastomosis to date. To our knowledge, the present study also included the largest subgroup of patients with Hinchey IV diverticulitis to date. Second, with regard to Hinchey III and Hinchey IV subgroups and preoperative disease classification, prediction of Hinchey classification by preoperative CT scanning is not very accurate (35). Previous trials have randomly assigned patients before the start of surgery, whereas in the present study, patients were randomised after diagnostic laparoscopy, thereby leading to a more accurate distinction between Hinchey grades. Hence, subgroup analyses for both Hinchey grades could also be done. We assumed centre-specific effects due to the multicentre setting to be small because of the low accrual rate per centre and the large number of hospitals. Finally, although we found no significant differences in quality-of-life scores between Hartmann's procedure and primary anastomosis, to our knowledge, this is the first randomised study to evaluate and compare these patient-reported outcomes for both treatment strategies, which have previously been shown to be important in survivors of perforated diverticulitis, particularly with regard to the presence of a stoma (36).

In conclusion, to our knowledge, this is the largest randomised trial comparing Hartmann's procedure with primary anastomosis in patients with perforated diverticulitis with purulent and faecal peritonitis. We found that primary anastomosis was superior to Hartmann's procedure with regard to 12-month stoma-free survival and overall morbidity after stoma reversal, with no significant differences in short-term morbidity and mortality after the index procedure. Therefore, in haemodynamically stable, immunocompetent patients, primary anastomosis is preferable to Hartmann's procedure for the treatment of perforated diverticulitis.

Research in context

Evidence before this study

We did a systematic literature search in PubMed for articles published from inception to Jan 17, 2019, with the keywords “diverticulitis”, “peritonitis”, “Hartmann*”, “primary”, and “anastomosis”, without language restrictions. We specifically included randomised controlled trials that compared Hartmann’s procedure with sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (Hinchey III or Hinchey IV); three of 127 articles identified by our search met this criterion. Quality assessment of these studies is given in the appendix (Figure 4). Overall, these trials randomly allocated 116 patients to primary anastomosis and 138 patients to Hartmann’s procedure, of whom 204 (80%) had Hinchey III diverticulitis. All three studies were prematurely terminated, either because of slow patient accrual (two studies) or for safety reasons (one study). No significant differences in mortality or overall morbidity were reported after the index procedure or reversal procedure. Two studies found a significant difference in stoma reversal rates in favour of primary anastomosis.

Added value of this study

To our knowledge, the LADIES trial is the largest study to date on primary anastomosis in Hinchey III and Hinchey IV diverticulitis and has several methodological differences compared with previous randomised trials. First, to our knowledge, this is the first trial to report on stoma-free survival as a primary endpoint and to incorporate patient-reported outcomes. Second, the decision to construct a defunctioning ileostomy was left to the discretion of the surgeon, whereas in previous studies, by design, a defunctioning ileostomy had to be constructed in all patients undergoing sigmoidectomy with primary anastomosis. However, in one previous trial, a third of patients underwent primary anastomosis without construction of an ileostomy, thereby deviating from the study protocol. Furthermore, patients in the present study were randomly assigned after diagnostic laparoscopy, allowing for a more accurate distinction between Hinchey III and Hinchey IV diverticulitis and, consequently, this is the first study to report on outcomes in Hinchey III and IV disease separately. Finally, although not all non-included patients could be registered during the trial period, baseline demographics and preoperative disease severity data for 235 eligible non-included patients were available to compare with included patients. This comparison improves the external generalisability of our study.

Implications of all the available evidence

The LADIES trial provides strong support in favour of sigmoidectomy with primary anastomosis as the most appropriate surgical treatment for diverticulitis with purulent or faecal peritonitis in patients who are haemodynamically stable and immunocompetent. This finding is important because, in combination with existing evidence, it has the potential to fundamentally change current practice and reduce both patient and socioeconomic burden.

Contributors

DPVL, SV, GDM, IMM, HAS, JV, WAB, and JFL contributed to study design or coordination. DPVL, SV, GDM, IMM, HAS, AGMH, EHJB, HBACS, QAJE, MFG, BA_vW, AAW_vG, RMPHC, SWN, MJPMG, SdS, AJLD, ECJC, WMU_vG, REGJMP, PMK, JAB_vdH, WHS, FC, JLMK, WAB, and JFL contributed to data acquisition. DPVL and SvD contributed to data analysis. DPVL, SV, GDM, IMM, HAS, JV, SvD, WAB, and JFL contributed to data interpretation. DPVL, WAB, and JFL drafted the report. All authors critically revised the content and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

If requested, deidentified data collected for the LADIES trial, the study protocol, and informed consent form can be made available. Please contact WAB (w.a.bemelman@amsterdamumc.nl) or JFL (j.lange@erasmusmc.nl), who will review all requests with the members of the Dutch Diverticular Disease (3D) Collaborative Study Group and the LADIES trial investigators. Requests should fulfil the following access criteria: research can only be conducted in collaboration with and after approval of the members of the 3D Collaborative Study Group and the LADIES trial investigators, and with a signed data access and sharing agreement. The members of the 3D Collaborative Study Group and the LADIES trial investigators must approve all research done with the shared data.

Acknowledgements

We thank all patients who were willing to participate in this trial and all staff of the participating hospitals for their efforts. The LADIES trial is part of a national consortium (the Dutch Diverticular Disease [3D] Collaborative Study Group).

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Tables

Table 1 Baseline patient and perioperative characteristics in the modified intention-to-treat population

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)
Patient characteristics		
Age (years)	61.7 (11.4)	62.4 (13.1)
Sex		
Female	25 (38%)	23 (36%)
Male	41 (62%)	41 (64%)
Body-mass index (kg/m ²)	28 (4.7)	26.3 (4.8)
American Society of Anesthesiologists score*		
I–II	37 (63%)	45 (76%)
III–IV	22 (37%)	14 (24%)
Previous diverticulitis	12 (18%)	12 (19%)
Previous laparotomy†	3 (5%)	1 (2%)
CT diagnosis	61 (92%)	60 (94%)
Hinchey grade IV	20 (30%)	18 (28%)
Preoperative disease severity		
Acute Physiology and Chronic Health Evaluation II score	8 (5–12)	7.5 (5–11)
POSSUM physiological score	20 (18–24)	20 (17–23)
POSSUM operative score	19 (19–20)	19 (19–20)
Portsmouth-POSSUM predicted mortality (%)	6 (4.4–15.0)	6.5 (3.8–11.2)
POSSUM predicted morbidity (%)	71.7 (64.1–86.6)	73 (61.1–82.1)
Mannheim peritonitis index	23 (17–27)	21 (17–26)
Interval from presentation to surgery (h)	8.0 (4.4–22.9)	9.4 (6.0–30.2)
C-reactive protein (mg/L)		
≤10	4 (6%)	6 (9%)
11–100	15 (23%)	13 (20%)
101–200	13 (20%)	15 (23%)
201–300	19 (29%)	10 (16%)
301–400	8 (12%)	9 (14%)
401–500	4 (6%)	6 (9%)
>500	2 (3%)	3 (5%)
Missing	1 (2%)	2 (3%)
White blood cell count (cells per µL)	14 600 (10 200–20 600)	14 200 (9000–16 900)
Operative characteristics		
Gastrointestinal surgeon present	57 (86%)	58 (91%)
Laparoscopic procedure	20 (30%)	17 (27%)
Operating time (min)	118.0 (95.5–135.3)	125.0 (110.0–154.0)
Drain placement‡	21 (32%)	27 (44%)
Anastomotic construction		
Manual	1 (2%)	11 (17%)
Stapler	0	43 (67%)
Missing	0	2 (3%)

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)
Anastomotic configuration		
End-to-end	0	18 (28%)
End-to-side	0	3 (5%)
Side-to-side	1 (2%)	9 (14%)
Side-to-end	0	20 (31%)
Missing	0	6 (9%)
Blood loss (mL)		
≤100	30 (45%)	31 (48%)
101–500	24 (36%)	20 (31%)
501–1000	3 (5%)	4 (6%)
>1000	0	1 (2%)
Missing	9 (14%)	8 (13%)

Data are mean (SD), n (%), or median (IQR). POSSUM=Physiological and operative severity score for the enumeration of mortality and morbidity.

*Missing in seven patients in the Hartmann's procedure group and five patients in the primary anastomosis group.

†One patient missing (Hinchey III).

‡One patient missing in Hinchey III group and one patient in Hinchey IV group.

Table 2 Morbidity outcomes after the index procedure

	Hartmann's procedure group (n=66)		Primary anastomosis group (n=64)		p value
	Patients	Events	Patients	Events	
Major morbidity	8 (12%)	16	9 (14%)	12	0.80
Surgical reintervention	4 (6%)	4	4 (6%)	5	..
Abscess with drainage	2 (3%)	5	2 (3%)	2	..
Fascial dehiscence	0	0	3 (5%)	3	..
Myocardial infarction	1 (2%)	1	0	0	..
Respiratory failure	4 (6%)	4	1 (2%)	1	..
Renal failure	3 (5%)	3	1 (2%)	1	..
Minor morbidity	26 (39%)	36	19 (30%)	21	0.27
Surgical site infection	8 (12%)	8	7 (11%)	7	..
Postoperative ileus	6 (9%)	6	7 (11%)	7	..
Pneumonia	5 (8%)	5	0	0	..
Delirium	5 (8%)	5	3 (5%)	3	..
Urinary tract infection or urine retention	2 (3%)	2	2 (3%)	2	..
Abscess without drainage	5 (8%)	5	0	0	..
Thrombosis	1 (2%)	1	0	0	..
Cardiac complications	4 (6%)	4	2 (3%)	2	..
Overall morbidity	29 (44%)	52	25 (39%)	33	0.60

Data are n (%). P values are for numbers of patients, not event numbers. Overall morbidity is major morbidity plus minor morbidity.

Table 3 Short-term postoperative outcomes of the index procedure

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=64)	p value
Postoperative admission to			0.53
Surgical ward	44 (67%)	40 (63%)	..
Post-anaesthesia care unit or medium care unit	4 (6%)	2 (3%)	..
ICU	18 (27%)	22 (34%)	..
Postoperative stay (days)	9.0 (7–15)	9.5 (7–13)	0.75
ICU stay (days)	2.0 (1–11)	1.5 (1–3)	0.18
Time until normal intake (days)	4.0 (1–6)	4.0 (2–6.8)	0.46

Data are n (%) or median (IQR). ICU=intensive care unit.

Table 4. Stoma outcomes

	Hartmann's procedure group (n=66)	Primary anastomosis group (n=63)	p value
Presence of stoma			
Without stoma	1 (2%)	17 (27%)	<0.0001
With stoma	65 (98%)	46 (73%)	..
Stoma reversal*	44 (68%)	38 (83%)	0.085
Ileostomy reversal	0	34 (89%)	..
Colostomy reversal (open)	24 (55%)	3 (8%)	..
Colostomy reversal (laparoscopic)	20 (45%)	1 (3%)	..

Data are n (%).

*One Hinchey III patient in the Hartmann's procedure group had an anastomotic leakage after Hartmann's reversal for which an end colostomy was constructed, which was not reversed before the end of the 12-month follow-up period. One Hinchey IV patient in the Hartmann's procedure group underwent open end colostomy reversal, during which it was decided to construct a protective loop ileostomy, which was reversed outside the 12-month follow-up period.

Table 5 Morbidity outcomes of the stoma reversal procedure

	Hartmann's procedure group (n=44)		Primary anastomosis group (n=38)		p value
	Patients	Events	Patients	Events	
Major morbidity	7 (16%)	9	1 (3%)	1	0.063
Surgical reintervention	4 (9%)	4	1 (3%)	1	..
Abscess with drainage	3 (7%)	3	0	0	..
Fascial dehiscence	1 (2%)	1	0	0	..
Myocardial infarction	1 (2%)	1	0	0	..
Respiratory failure	0	0	0	0	..
Renal failure	0	0	0	0	..
Minor morbidity	6 (14%)	6	2 (5%)	2	0.28
Surgical site infection	5 (11%)	5	1 (3%)	1	..
Postoperative ileus	0	0	1 (3%)	1	..
Pneumonia	0	0	0	0	..
Delirium	0	0	0	0	..
Urinary tract infection or urine retention	1 (2%)	1	0	0	..
Abscess without drainage	0	0	0	0	..
Thrombosis	0	0	0	0	..
Cardiac complications	0	0	0	0	..
Overall morbidity	13 (30%)	15	3 (8%)	3	0.023

Data are n (%). Morbidity was scored in the first 30 days after reversal, or during admission for stoma reversal if still in hospital after 30 days.

Table 6 Short-term postoperative outcomes of the index procedure and (if applicable) reversal procedure combined

	Hartmann's procedure group (n=66)		Primary anastomosis group (n=63*)		p value
	Patients	Events	Patients	Events	
Major morbidity	15 (23%)	25	9 (14%)	13	0.26
Surgical reintervention	8 (12%)	10	5 (8%)	6	..
Abscess with drainage	5 (8%)	5	2 (3%)	2	..
Fascial dehiscence	1 (2%)	1	3 (5%)	3	..
Myocardial infarction	2 (3%)	2	0	0	..
Respiratory failure	4 (6%)	4	1 (2%)	1	..
Renal failure	3 (5%)	3	1 (2%)	1	..
Minor morbidity	30 (45%)	42	19 (30%)	23	0.10
Surgical site infection	12 (18%)	13	7 (11%)	8	..
Postoperative ileus	6 (9%)	6	8 (13%)	8	..
Pneumonia	5 (8%)	5	0	0	..
Delirium	5 (8%)	5	3 (5%)	3	..
Urinary tract infection or urine retention	3 (5%)	3	2 (3%)	2	..
Abscess without drainage	5 (8%)	5	0	0	..
Thrombosis	1 (2%)	1	0	0	..
Cardiac complications	4 (6%)	4	2 (3%)	2	..
Overall morbidity	37 (56%)	67	25 (40%)	36	0.078

Data are n (%). P values are from statistical comparison of numbers of patients, not event numbers. Overall morbidity is major morbidity plus minor morbidity.

*One patient lost to follow-up after providing data for short-term outcomes for the index procedure only.

Figures

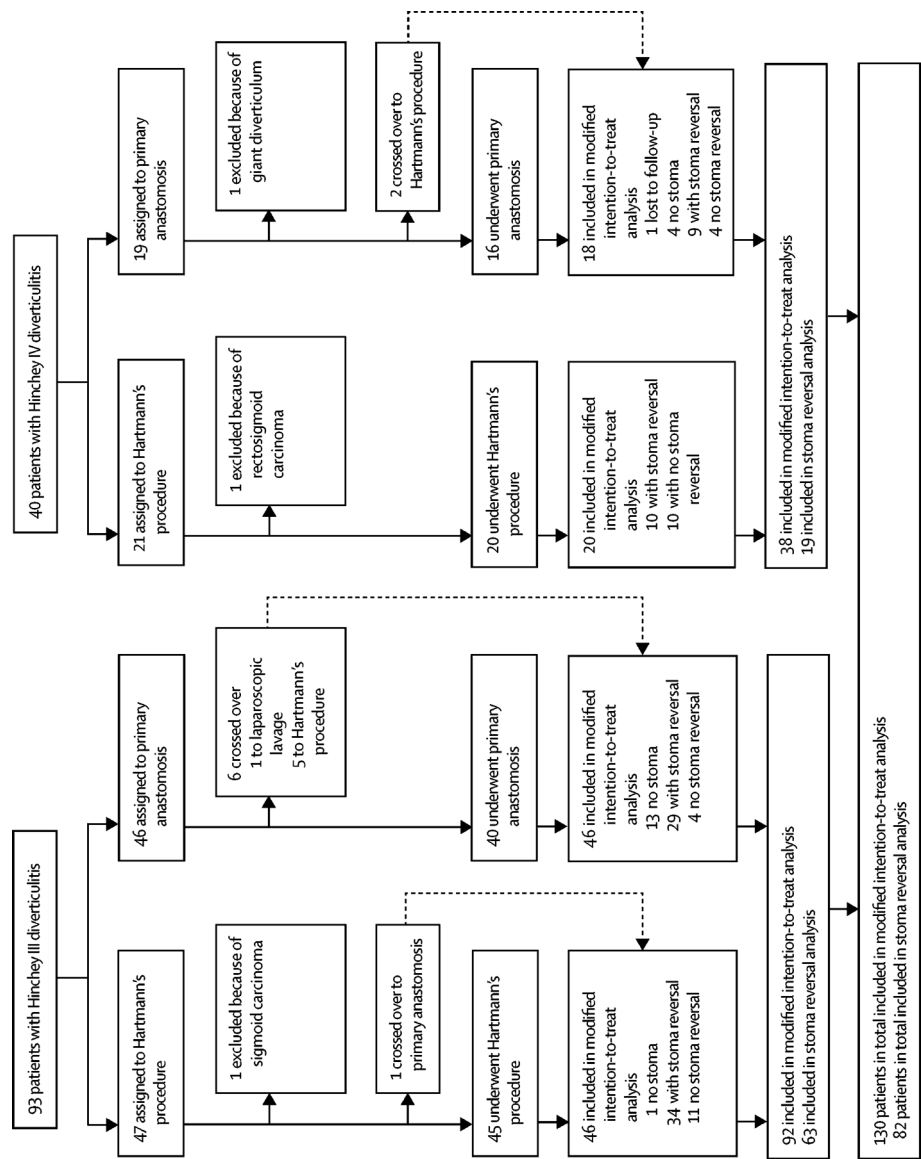


Figure 1 Trial profile

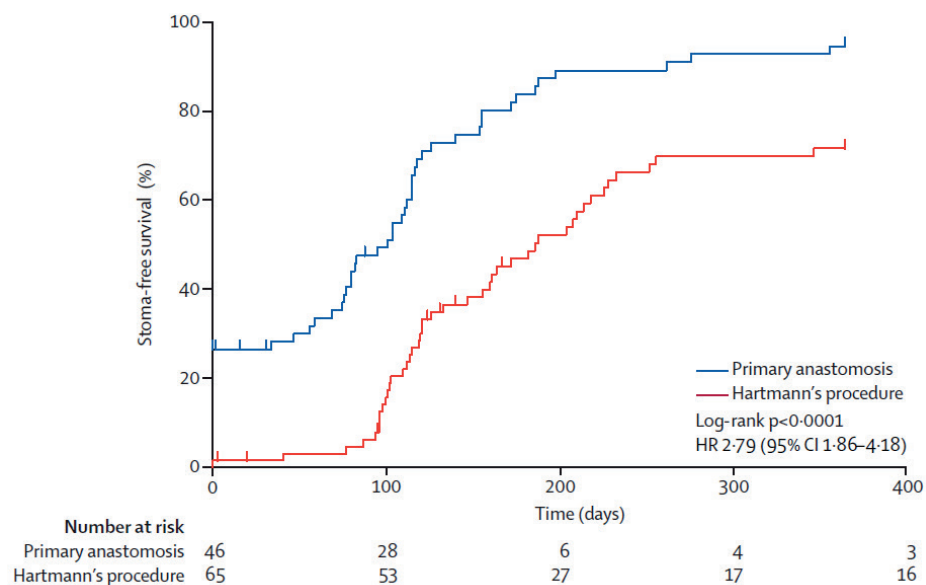


Figure 2 Kaplan-Meier graph of 12-month stoma-free survival

Appendix

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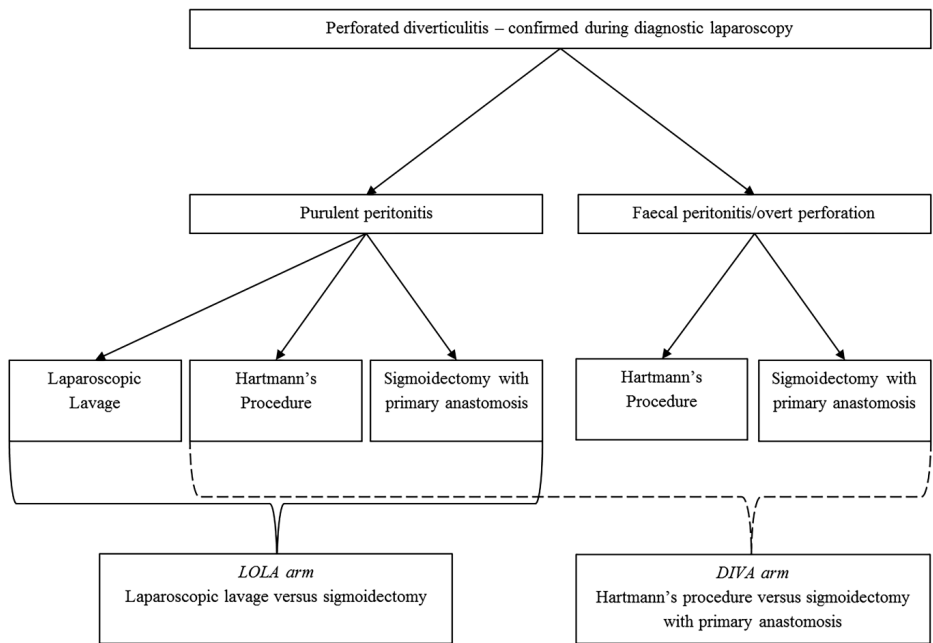
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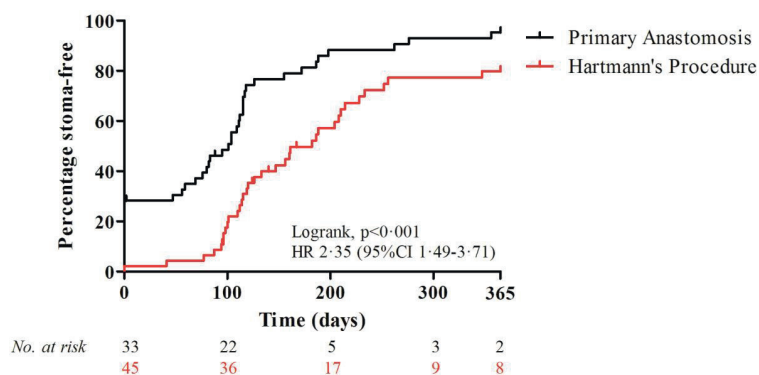
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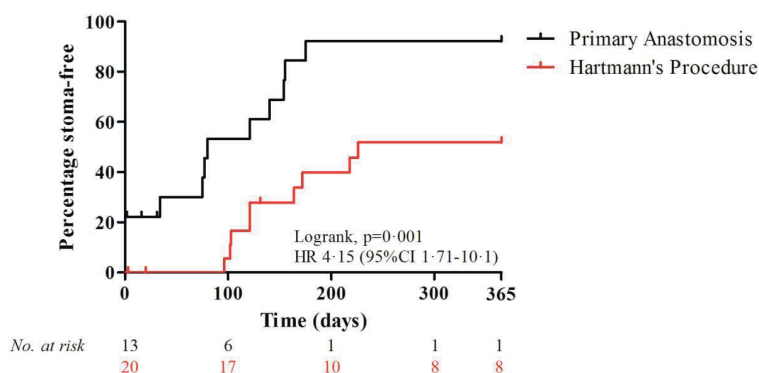
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Supplemental Figure 1 Trial design



Supplemental Figure 2 Stoma-free survival (Hinchey III)



Supplemental Figure 3 Stoma-free survival (Hinchey IV)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Binda 2012	+	-	-	?	+	+	?
Bridoux 2017	+	-	-	?	+	+	?
Oberkofler 2012	+	-	-	?	+	+	?

Supplemental Figure 4 Risk of Bias assessment

Supplemental Table 1 Hinchey classification

Hinchey classification	
I	Pericolic abscess or phlegmon
II	Pelvic, intra-abdominal, or retroperitoneal abscess
III	Generalised purulent peritonitis
IV	Generalised faecal peritonitis

Supplemental Table 2 Reasons for cross-over

Hartmann's Procedure to Primary Anastomosis	
<i>Hinchey III</i>	
- Obese patient, ostomy not desirable (n = 1)	
<i>Hinchey IV</i>	
- None	
Primary Anastomosis to Hartmann's Procedure	
<i>Hinchey III</i>	
- Serosal layer rectum damaged (n = 2)	
- Doubts on tissue quality (n = 3)	
<i>Hinchey IV</i>	
- Doubts on tissue quality (n = 1)	
- Fear of blow-out (n = 1)	
Primary Anastomosis to Laparoscopic Lavage	
<i>Hinchey III</i>	
- Recent knee replacement – not possible to be positioned in stirrups (n = 1)	
<i>Hinchey IV</i>	
- None	

Supplemental Table 3 Inclusion numbers per centre

	Hartmann's Procedure (n=66)	Primary Anastomosis (n=64)	Total (n=130)
Tergooi Hospital	5 (7.6)	8 (12.5)	13 (10)
Orbis Medical Centre*	5 (7.6)	7 (10.9)	12 (9.2)
University Medical Centre Amsterdam, AMC	6 (9.1)	5 (7.8)	11 (8.5)
Amphia Hospital	4 (6.1)	6 (9.4)	10 (7.7)
Atrium Medical Centre*	6 (9.1)	3 (4.7)	9 (6.9)
Catharina Hospital	3 (4.5)	6 (9.4)	9 (6.9)
Westfries Hospital**	5 (7.6)	3 (4.7)	8 (6.2)
Maggiore Hospital (Bologna, Italy)	4 (6.1)	3 (4.7)	7 (5.4)
OLVG	4 (6.1)	3 (4.7)	7 (5.4)
Kennemer Hospital†	3 (4.5)	3 (4.7)	6 (4.6)
Spaarne Hospital†	2 (3.0)	2 (3.1)	4 (3.1)
University Hospitals Leuven	1 (1.5)	3 (4.7)	4 (3.1)
Isala Hospital	2 (3.0)	1 (1.6)	3 (2.3)
Gelderse Vallei Hospital	2 (3.0)	1 (1.6)	3 (2.3)
Lucas Andreas Hospital§	1 (1.5)	2 (3.1)	3 (2.3)
Meander Medical Centre	1 (1.5)	2 (3.1)	3 (2.3)
University Medical Centre Utrecht	2 (3.0)	1 (1.6)	3 (2.3)
Albert Schweitzer Hospital	1 (1.5)	1 (1.6)	2 (1.5)
Haga Hospital	1 (1.5)	1 (1.6)	2 (1.5)
Maggiore Hospital (Parma, Italy)	0	2 (3.1)	2 (1.5)
VieCuri Medical Centre	2 (3.0)	0	2 (1.5)
Elisabeth-TweeSteden Hospital	1 (1.5)	0	1 (0.8)
Erasmus University Medical Centre	1 (1.5)	0	1 (0.8)
Flevo Hospital	0	1 (1.6)	1 (0.8)
Maastricht University Medical Centre	1 (1.5)	0	1 (0.8)
Reinier de Graaf Hospital	1 (1.5)	0	1 (0.8)
Rode Kruis Hospital	1 (1.5)	0	1 (0.8)
St. Antonius Hospital	1 (1.5)	0	1 (0.8)

Data are n (%).

*Now part of Zuyderland Medical Centre.

**Now known as Dijklander Hospital.

†Now part of Spaarne Gasthuis.

§Now part of OLVG.

Supplemental Table 4 Baseline patient and perioperative characteristics for both Hinchey grades

	Hinchey III (n=92)	Hinchey IV (n=38)	p value
Age (years)	61.8 (12.2)	62.8 (12.3)	0.663
Sex (male/female)	62/30 (67.4/32.6)	20/18 (52.6/47.4)	0.161
BMI (kg/m ²)	27.1 (4.8)	27.3 (5.1)	0.820
ASA I-II	59 (70.2)	23 (67.6)	0.827
ASA III-IV	25 (29.8)	11 (32.4)	
Previous diverticulitis	19 (20.7)	5 (13.2)	0.456
Previous laparotomy*	3 (3.3)	1 (2.6)	1.000
CT diagnosis	88 (95.7)	33 (86.8)	0.122
Preoperative disease severity			
APACHE II	7.5 (5-11)	8 (5.8-11.3)	0.491
POSSUM PS	19 (17.3-23)	20 (17-25)	0.548
POSSUM OS	19 (19-20)	19 (19-20)	0.666
P-POSSUM predicted mortality (%)	6.1 (4.1-11.3)	7 (4.2-16.1)	0.585
POSSUM predicted morbidity (%)	71.4 (61.1-82.4)	74.3 (63.4-87.6)	0.510
Mannheim Peritonitis Index	21 (17-22)	27.5 (23-32)	<0.001
Interval from presentation to surgery (hours)	9.4 (5.7-27)	7.2 (4.7-33.3)	0.440
C-reactive protein (mg/L)			
<10	5 (5.4)	5 (13.2)	0.700
11-100	20 (21.7)	8 (21.1)	
101-200	20 (21.7)	9 (23.7)	
201-300	23 (25)	6 (15.8)	
301-400	13 (14.1)	4 (10.5)	
401-500	7 (7.6)	3 (7.9)	
>500	3 (3.3)	2 (5.3)	
Missing	1 (1.1)	1 (2.6)	
White blood cell count (x10 ⁹ /L)	14.3 (9.6-18)	15.4 (9.7-20.1)	0.725
Operative characteristics			
GI surgeon present	81 (88.0)	34 (89.5)	1.000
Laparoscopic procedure	30 (32.6)	7 (18.4)	0.135
Operating time (minutes)	120 (100-142)	126 (107-164)	0.346
Drain placement**	56 (61.5)	24 (64.9)	0.841
Blood loss (mL)			
<100	45 (48.9)	16 (42.1)	0.800
101-500	29 (31.5)	15 (39.5)	
501-999	5 (5.4)	2 (5.3)	
>1000	1 (1.1)	0	
Missing	12 (13)	5 (13.2)	
Postoperative care			
Surgical ward	63 (68.5)	21 (55.3)	0.192
PACU or MCU	5 (5.4)	1 (2.6)	
ICU	24 (26.1)	16 (42.1)	

* One patient missing (Hinchey III)

** One patient missing in Hinchey III group and one patient in Hinchey IV group

Data are n (%), mean (SD), or median (IQR). ASA=American Society of Anesthesiologists score; APACHE II= Acute Physiology and Chronic Health Evaluation II; POSSUM PS/OS= Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; PACU=Post Anesthesia Care Unit; MCU=Medium Care Unit; ICU=Intensive Care unit.

Supplemental Table 5 Baseline patient and perioperative characteristics in both treatment groups (subdivided by Hinchev grade)

	Hinchev III			Hinchev IV		
	HP (n=46)	PA (n=46)	p value	HP (n=20)	PA (n=18)	p value
Age (years)	61.5 (11.8)	62.1 (12.8)	0.804	62.4 (10.7)	63.3 (14.2)	0.834
Sex (male/female)	29/17 (63/37)	33/13 (72/28)	0.505	12/8 (60/40)	8/10 (44/56)	0.516
BMI (kg/m ²)	27.7 (4.8)	26.4 (4.8)	0.209	28.7 (4.7)	25.7 (5.2)	0.096
ASA I-II	33 (78.6)	26 (61.9)	0.151	12 (70.6)	11 (64.7)	1.000
ASA III-IV	9 (21.4)	16 (38.1)		5 (29.4)	6 (35.3)	
Previous diverticulitis	10 (21.7)	9 (19.6)	1.000	2 (10)	3 (16.7)	0.653
Previous laparotomy*	2 (2.2)	1 (4.3)	1.000	1 (5)	0	1.000
CT diagnosis	42 (91.3)	46 (100)	0.117	19 (95)	14 (77.8)	0.170
Preoperative disease severity						
APACHE II	8 (4.12)	7 (5.10.3)	0.452	8 (6.3-13.3)	8 (4.11.3)	0.303
POSSUM PS	19 (17.8-23)	19.5 (17-23)	0.681	20.5 (18-29.5)	20 (16-23.3)	0.217
POSSUM OS	19 (19-20)	19 (19-20)	0.823	20 (19-20)	19 (19-20)	0.251
P-POSSUM predicted mortality (%)	6 (4.2-11.3)	6.5 (3.9-11.2)	0.963	7.1 (4.6-26.9)	6.6 (3.6-10.1)	0.206
POSSUM predicted morbidity (%)	71.1 (61.2-82.3)	73 (60.9-82.5)	0.919	74.6 (65.5-92.9)	72.7 (59.9-80.9)	0.206
Mannheim Peritonitis Index	21 (17-26)	19 (17-22)	0.245	27 (23-31.5)	28 (23-32)	0.740
Interval from presentation to surgery (hours)	9 (4.5-25.8)	9.4 (6.3-28.5)	0.637	6.3 (4.3-22)	8.3 (5.5-41.3)	0.350
C-reactive protein (mg/L)						
<10	1 (2.2)	4 (8.7)	0.143	3 (15)	2 (11.1)	
11-100	11 (23.9)	9 (19.6)		4 (20)	4 (22.2)	0.707
101-200	10 (21.7)	10 (21.7)		3 (15)	6 (33.3)	
201-300	16 (34.8)	7 (15.2)		3 (15)	3 (16.7)	
301-400	6 (13)	7 (15.2)		2 (10)	2 (11.1)	
401-500	1 (2.2)	6 (13)		3 (15)	0	
>500	1 (2.2)	2 (4.3)		1 (5)	1 (5.6)	
Missing	0	1 (2.2)		1 (5)	0	
White blood cell count (x10 ⁹ /L)	14.6 (9.6-20.5)	14 (9.5-17.6)	0.394	17.4 (11.5-21.7)	14.7 (6-16.9)	0.251

	Hinchey III		Hinchey IV	
	HP (n=46)	PA (n=46)	HP (n=20)	PA (n=18)
Operative characteristics				
GI surgeon present	40 (87)	41 (89.1)	17 (85)	17 (94.4)
Laparoscopic procedure	16 (34.8)	14 (30.4)	4 (20)	3 (16.7)
Operating time (minutes)	115.5 (92.5-133.8)	125 (110-150)	122.5 (106.5-143)	127 (108-181)
Drain placement**	16 (34.8)	19 (42.2)	5 (25)	8 (47.1)
Blood loss (mL)				
<100	22 (47.8)	23 (50)	8 (40)	8 (44.4)
101-500	16 (34.8)	13 (28.3)	8 (40)	7 (38.9)
501-999	1 (2.2)	4 (8.7)	2 (10)	0
>1000	0	1 (2.2)	0	0
Missing	7 (15.2)	5 (10.9)	2 (10)	3 (16.7)

* 1 Hinchey III PA patient missing

** 1 Hinchey III PA patient missing; 1 Hinchey IV PA patient missing

Data are n (%), mean (SD), or median (IQR). ASA=American Society of Anesthesiologists score; APACHE II= Acute Physiology and Chronic Health Evaluation II; POSSUM PS/OS= Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity.

Supplemental Table 6 Characteristics of included and eligible non-included patients

	Non-included patients (n=235)	Included in DIVA arm (n=130)	p value
Age (years)	62.7 (13.5)	62.2 (12.2)	0.668
Sex (male/female)	119/116 (50.6/49.4)	82/48 (63.1/36.9)	0.028
BMI (kg/m ²)	26.6 (23.7-29.7)	26.5 (24-30.8)	0.847
ASA I-II	98 (65.3)	82 (69.5)	0.514
ASA III-IV	52 (34.7)	36 (30.5)	
Previous diverticulitis	45 (19.4)	24 (18.5)	0.890
Previous laparotomy	21 (9.1)	4 (3.1)	0.032
CT diagnosis	191 (84.9)	121 (93.1)	0.027
Preoperative disease severity			
APACHE II	7 (5-11)	8 (5-11)	0.218
POSSUM PS	19 (16-24)	20 (17-23)	0.038
POSSUM OS	19 (19-20)	19 (19-20)	<0.001
P-POSSUM predicted mortality (%)	4.4 (2.8-11.6)	6.1 (4.3-11.3)	0.011
POSSUM predicted morbidity (%)	64.8 (52.5-82.4)	71.7 (61.2-82.3)	0.003
Mannheim Peritonitis Index	22 (17-24)	22 (17-26.3)	0.423
Interval from presentation to surgery (hours)	13.5 (6-43.8)	8.8 (5.3-29.3)	0.016
Operative characteristics			
Hinchey III/IV	158/77 (67.2/32.8)	92/38 (70.8/29.2)	0.557
GI surgeon present	158 (68.7)	115 (88.5)	<0.001
Laparoscopic procedure	44 (18.7)	37 (28.5)	0.036
Operating time (minutes)	98 (67.5-129.5)	120 (105-143)	<0.001
Laparoscopic lavage	41 (17.4)	1 (0.8)	<0.001
Hartmann's procedure	164 (69.8)	72 (55.4)	
Sigmoidectomy with primary anastomosis	30 (12.8)	57 (43.8)	
<i>Without stoma construction</i>	14 (46.7)	17 (29.8)	
Outcomes			
In-hospital mortality	20 (8.5)	6 (4.6)	0.205
Length of follow-up (months)	18 (11-29)	12 (12-12)	<0.001
Stoma-free and alive	139 (61.5)	97 (75.2)	0.010

Data are n (%), mean (SD), or median (IQR). ASA=American Society of Anesthesiologists score; APACHE II= Acute Physiology and Chronic Health Evaluation II; POSSUM PS/OS= Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; PACU=Post Anesthesia Care Unit; MCU=Medium Care Unit; ICU=Intensive Care unit.

Supplemental Table 7 90-day Clavien-Dindo scores following the index procedure

	Hartmann's Procedure (n=66)	Primary Anastomosis (n=63)	p value
Clavien-Dindo			
No complications	25 (37.9)	26 (41.3)	0.677
Grade I	7 (10.6)	13 (20.6)	
Grade II	19 (28.8)	11 (17.5)	
Grade IIIa	3 (4.5)	4 (6.3)	
Grade IIIb	7 (10.6)	5 (7.9)	
Grade IVa	1 (1.5)	1 (1.6)	
Grade IVb	2 (3)	1 (1.6)	
Grade V	2 (3)	2 (3.2)	
≥ Grade IIIb	12 (18.2)	9 (14.3)	0.636

Data are n (%).

Supplemental Table 8 Comparison of short-term postoperative outcomes of the index procedure (subdivided by Hinchey grade)

	Hinchey III						Hinchey IV					
	HP (n=46)			PA (n=46)			HP (n=20)			PA (n=18)		
	Patients	Events		Patients	Events	p value	Patients	Events		Patients	Events	p value
Major morbidity	2 (4.3)	6		6 (13)	7	0.267	6 (30)	11		3 (16.7)	5	0.454
Surgical reintervention	1 (2.2)	1		2 (4.3)	2		3 (15)	3		2 (11.1)	3	
Abscess with drainage	0	0		1 (2.2)	1		2 (10)	5		1 (5.6)	1	
Fascial dehiscence	0	0		3 (6.5)	3		0	0		0	0	
Myocardial infarction	1 (2.2)	1		0	0		0	0		0	0	
Respiratory failure	2 (4.3)	2		1 (2.2)	1		2 (10)	2		0	0	
Renal failure	2 (4.3)	2		0	0		1 (5)	1		1 (5.6)	1	
Minor morbidity	17 (37)	20		14 (30.4)	15	0.659	9 (45)	16		5 (27.8)	6	0.328
Surgical site infection	6 (13)	6		5 (10.9)	5		2 (10)	2		2 (11.1)	2	
Postoperative ileus	2 (4.3)	2		5 (10.9)	5		4 (20)	4		2 (11.1)	2	
Pneumonia	4 (8.7)	4		0	0		1 (5)	1		0	0	
Delirium	3 (6.5)	3		3 (6.5)	3		2 (10)	2		0	0	
UTI/retention	1 (2.2)	1		1 (2.2)	1		1 (5)	1		1 (5.6)	1	
Abscess without drainage	3 (6.5)	3		0	0		2 (10)	2		0	0	
Thrombosis	0	0		0	0		1 (5)	1		0	0	
Cardiac complications	1 (2.2)	1		1 (2.2)	1		3 (15)	3		1 (5.6)	1	
Overall morbidity	17 (37)	26		17 (37)	22	1.000	12 (60)	27		8 (44.4)	11	0.516
Mortality	0			1 (2.2)		1.000	2 (10)			3 (16.7)		0.653
Primary hospital stay												
Postoperative admission to:												
Surgical ward	34 (73.9)			29 (63)		0.105	10 (50)			11 (61.1)		0.412
PACU or MCU	4 (8.7)			1 (2.2)			0			1 (5.6)		
ICU	8 (17.4)			16 (34.8)			10 (50)			6 (33.3)		
Postoperative stay (days)	9 (6.12)			9.5 (7-13.3)		0.463	11.5 (8.3-18.5)			9.5 (6-13.2)		0.126
ICU stay (days)	2 (1.4)			1 (1-2.3)		0.296	2.5 (1-19.5)			3.5 (1-16.5)		0.875
Days until normal intake	3 (1.5)			4 (2-7.3)		0.175	5 (3-7)			4.5 (1-6.3)		0.536

Data are n (%) or median (IQR). P values resulted from the statistical comparison of the number of patients, not event numbers. Overall morbidity=major + minor morbidity. UTI=urinary tract infection; PACU=Post Anesthesia Care Unit; MCU=Medium Care Unit; ICU=Intensive Care unit.

Supplemental Table 9 Characteristics and outcomes of patients allocated to primary anastomosis: primary anastomosis with ileostomy *versus* without ileostomy

	No ileostomy (n=17)	Ileostomy (n=40)	p value
Age (years)	60.3 (3.2)	63.1 (2.1)	0.464
Sex (male/female)	12/5 (70.6-4/29.4)	24/16 (60/40)	0.555
BMI (kg/m ²)	27.4 (1.2)	25.6 (0.8)	0.237
ASA I-II	13 (76.5)	19 (54.2)	0.143
ASA III-IV	4 (23.5)	16 (45.7)	
Previous diverticulitis	1 (5.9)	9 (22.5)	0.253
Previous laparotomy	0	1 (2.5)	1.000
CT diagnosis	17 (100)	36 (90)	0.306
Preoperative disease severity			
APACHE II	7 (4-8.5)	8 (6-11)	0.261
POSSUM PS	18 (16-23.5)	20 (18-23)	0.156
POSSUM OS	20 (19-20)	19 (19-20)	0.365
P-POSSUM predicted mortality (%)	4.4 (3.4-12.3)	7 (4.4-11.3)	0.299
POSSUM predicted morbidity (%)	64.1 (58.4-83.7)	74.3 (64.1-82.4)	0.407
Mannheim Peritonitis Index	18 (17-22)	22 (17-26)	0.172
Interval from presentation to surgery (hours)	9.4 (2.6-30.3)	9.3 (6.1-30)	0.919
C-reactive protein (mg/L)			
<10	3 (17.6)	3 (7.5)	0.382
11-100	2 (11.8)	11 (27.5)	
101-200	6 (35.3)	9 (22.5)	
201-300	1 (5.9)	7 (17.5)	
301-400	4 (23.5)	4 (10)	
401-500	1 (5.9)	3 (7.5)	
>500	0	2 (5)	
Missing	0	1 (2.5)	
White blood cell count (x10 ⁹ /L)	14.1 (12.1-16.3)	14.1 (8.9-17)	0.910
Operative characteristics			
GI surgeon present	15 (88.2)	36 (90)	1.000
Laparoscopic procedure	4 (23.5)	12 (30)	0.753
Operating time (minutes)	120 (105-154)	126.5 (114-150)	0.428
Drain placement	12 (70.6)	18 (46.2)	0.145
Blood loss (mL)			
<100	7 (41.2)	21 (52.5)	0.345
101-500	7 (41.2)	11 (27.5)	
501-999	1 (5.9)	2 (5)	
>1000	1 (5.9)	0	
Missing	1 (5.9)	6 (15)	
Outcomes			
Major morbidity	2 (11.8)	5 (12.5)	1.000
Minor morbidity	2 (11.8)	15 (37.5)	0.064
Overall morbidity	4 (23.5)	18 (45.0)	0.150
Mortality	0	3 (7.5)	0.547
Postoperative stay (days)	7 (11-14)	11 (7-14)	0.013

Data are n (%), mean (SD), or median (IQR). ASA=American Society of Anesthesiologists score; APACHE II= Acute Physiology and Chronic Health Evaluation II; POSSUM PS/OS= Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity.

Supplemental Table 10 Stoma outcomes and comparison of short-term outcomes of the stoma reversal procedure (as subdivided by Hinchey grade)

	Hinchey III				Hinchey IV			
	HP (n=46)	PA (n=46)	p value	HP (n=20)	PA (n=17)	p value		
Without stoma	1 (2-2)	13 (28-3)	0.001	0	4 (23-5)	0.036		
With stoma	45 (97-8)	33 (71-7)		20 (100)	13 (76-5)			
Stoma reversal*	34/45 (75-6)	29/33 (84-8)	0.247	10/20 (50)	9/13 (69.2)	0.310		
Ileostomy reversal	0	25 (86-2)		0	9 (100)			
Colostomy reversal (open)	17 (50)	3 (10-3)		7 (70)	0			
Colostomy reversal (lap)	17 (50)	1 (3-4)		3 (30)	0			
Postoperative outcomes	HP (n=34)	PA (n=29)		HP (n=10)	PA (n=9)			
	Patients	Events	Patients	Events	Patients	Events	p value	
Major morbidity	5 (14.7)	6	1 (3-5)	1	2 (20)	3	0.205	
Surgical reintervention	3 (8.8)	3	1 (3-5)	1	1 (10)	1	0	
Abscess with drainage	3 (8.8)	3	0	0	0	0	0	
Fascial dehiscence	0	0	0	0	1 (10)	1	0	
Myocardial infarction	0	0	0	0	1 (10)	1	0	
Respiratory failure	0	0	0	0	0	0	0	
Renal failure	0	0	0	0	0	0	0	
Minor morbidity	5 (14.7)	5	2 (6-9)	2	1 (10)	1	0.437	
Surgical site infection	4 (11.8)	4	1 (3-5)	1	1 (10)	1	0	
Postoperative ileus	0	0	1 (3-5)	1	0	0	0	
Pneumonia	0	0	0	0	0	0	0	
Delirium	0	0	0	0	0	0	0	
UTI/retention	1 (2.9)	1	0	0	0	0	0	
Abscess without drainage	0	0	0	0	0	0	0	
Thrombosis	0	0	0	0	0	0	0	
Cardiac complications	0	0	0	0	0	0	0	
Overall morbidity	10 (29.4)	11	3 (10.3)	3	3 (30)	4	0.116	
Mortality	0	0	0	0	0	0	0.211	
Interval to reversal (days)	133 (100.5-206)		112 (82.5-163.5)		142.5 (102.8-218.3)		0	
Postoperative stay (days)	5 (4-6)		4 (2.5-5)		5.5 (3.8-8.8)		0	
							0.133	
							0.243	

*One Hinchey III patient in the Hartmann's procedure group had an anastomotic leakage after Hartmann's reversal for which an end colostomy was constructed, which was not reversed before the end of the 12-month follow-up period. One Hinchey IV patient in the Hartmann's procedure group underwent open end colostomy reversal, during which it was decided to construct a protective loop ileostomy, which was reversed outside of the 12-month follow-up period.

Data are n (%) and median (IQR). Morbidity and mortality were scored in the first 30 days post-reversal, or during admission for stoma reversal if still admitted beyond 30 days.

Supplemental Table 11 Reasons for not reversing stoma within twelve-month follow-up period

Hartmann's Procedure (n=21)
<i>Hinchey III (n=11)</i>
- Preference of patient to keep stoma (n=1)
- No approval of surgeon (n=1)
- Deceased before reversal (n=4)
- Unknown reason (n=5)
<i>Hinchey IV (n=10)</i>
- Preference of patient to keep stoma (n=1)
- Patient not seen back (n=1)
- No approval cardiologist (n=1)
- Patient agreed to surgeon's advice to not reverse (age) (n=1)
- Deceased before reversal (n=3)
- Unknown reason (n=3)
Primary Anastomosis (n=8)
<i>Hinchey III (n=4)</i>
- Preference of patient to keep stoma (n=1)
- Deceased before reversal (n=2)
- Unknown reason (n=1)
<i>Hinchey IV (n=4)</i>
- No approval of surgeon (n=1)
- Deceased before reversal (n=2)
- Unknown reason (n=1)

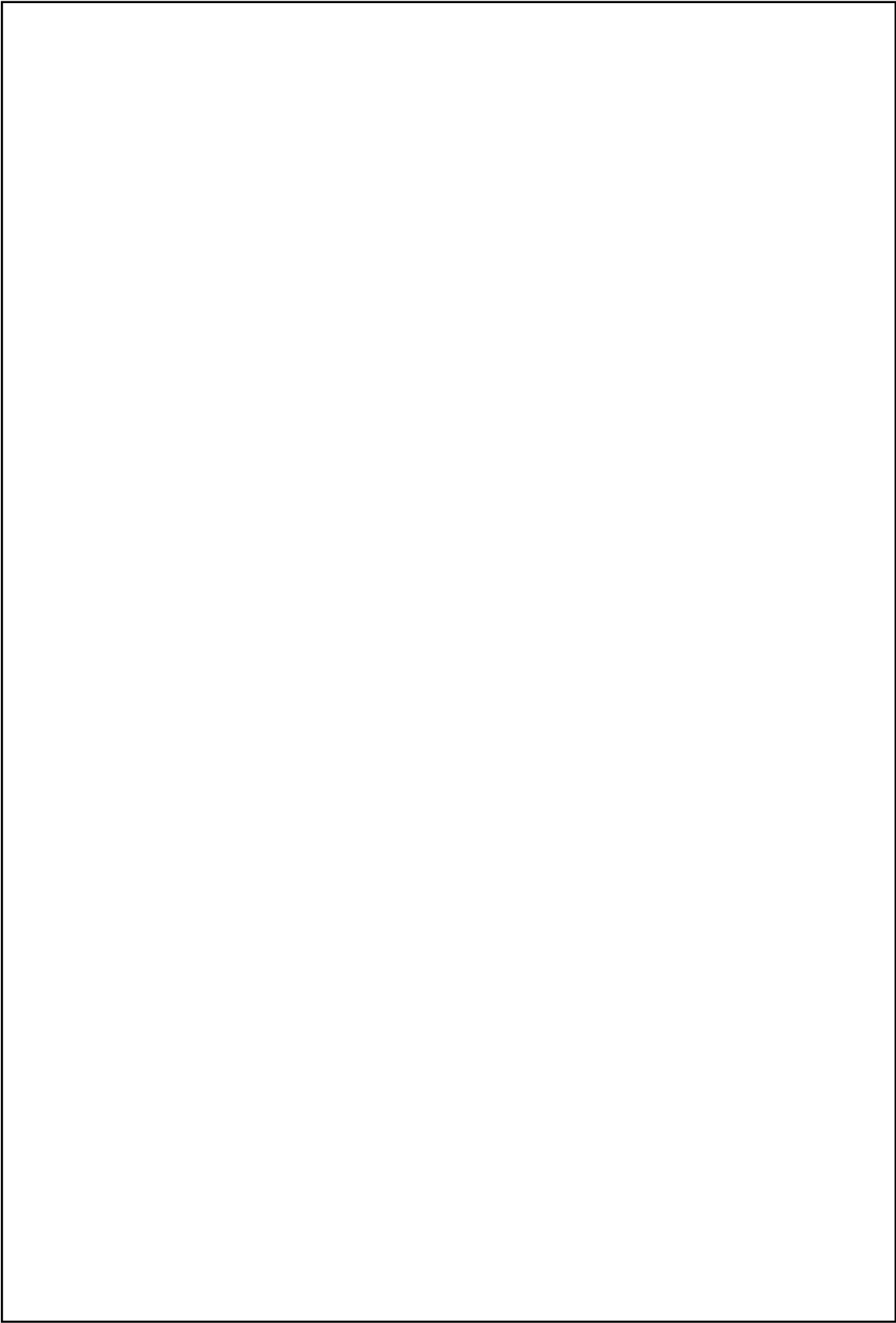
Supplemental Table 12 Quality of life outcomes

	Hartmann's procedure					Primary anastomosis					p-value*				
	2w	4w	3m	6m	12m	2w	4w	3m	6m	12m	2w	4w	3m	6m	12m
SF-36v2															
Physical component score	34.5	36.3	41.2	43.6	47.9	31.2	37.2	42.9	45.3	48.4	0.540	0.870	0.870	0.870	0.873
Mental component score	42.4	42.7	47.0	47.3	47.9	45.1	45.7	50.1	51.1	48.0	0.870	0.870	0.870	0.570	0.973
GIQLI															
Physical wellbeing	11.4	13.3	15.0	16.5	16.9	10.6	13.8	15.6	17.3	17.4	0.870	0.870	0.873	0.873	0.870
GI symptoms	60.11	62.8	64.0	64.3	64.5	58.1	63.4	64.2	64.4	64.5	0.870	0.870	0.895	0.973	0.985
Social wellbeing	6.5	7.9	10.1	12.1	13.8	5.7	8.6	11.5	13.4	14.1	0.870	0.870	0.870	0.870	0.873
Emotional wellbeing	11.5	12.9	13.8	14.5	15.1	12.2	13.8	14.3	15.8	15.5	0.870	0.870	0.870	0.870	0.870
Total score	89.5	96.9	102.9	107.5	110.2	86.6	99.6	105.6	110.9	111.5	0.870	0.870	0.870	0.870	0.870
EQ-5D-3L															
Health state	0.51	0.60	0.71	0.77	0.80	0.53	0.72	0.78	0.83	0.84	0.910	0.570	0.870	0.870	0.870
VAS	54.6	61.9	65.7	72.4	73.3	53.7	65.2	69.8	71.6	79.0	0.915	0.870	0.870	0.915	0.870

*After correction for multiple testing with the Benjamini-Hochberg method.

Supplemental Table 13 Questionnaire response rates

	Group	Observed	Died	Missing
SF-36v2	<i>2 weeks</i>	HP (n=66) 42 (63.6)	1 (1.5)	23 (34.9)
		PA (n=64) 40 (62.5)	3 (4.7)	21 (32.8)
	<i>4 weeks</i>	HP (n=66) 41 (62.1)	2 (3.0)	23 (34.9)
		PA (n=64) 42 (65.6)	4 (6.3)	18 (28.1)
	<i>3 months</i>	HP (n=66) 39 (59.1)	2 (3.0)	25 (37.9)
		PA (n=64) 40 (62.5)	5 (7.8)	19 (29.7)
	<i>6 months</i>	HP (n=66) 31 (47.0)	7 (10.6)	28 (42.4)
		PA (n=64) 38 (59.4)	5 (7.8)	21 (32.8)
	<i>12 months</i>	HP (n=66) 13 (19.7)	7 (10.6)	46 (69.7)
		PA (n=64) 8 (12.5)	5 (7.8)	51 (79.7)
GIQLI	<i>2 weeks</i>	HP (n=66) 41 (62.1)	1 (1.5)	24 (36.4)
		PA (n=64) 40 (62.5)	3 (4.7)	21 (32.8)
	<i>4 weeks</i>	HP (n=66) 41 (62.1)	2 (3.0)	23 (34.9)
		PA (n=64) 42 (65.6)	4 (6.3)	18 (28.1)
	<i>3 months</i>	HP (n=66) 38 (57.6)	2 (3.0)	26 (39.4)
		PA (n=64) 40 (62.5)	5 (7.8)	19 (29.7)
	<i>6 months</i>	HP (n=66) 31 (47)	7 (10.6)	28 (42.4)
		PA (n=64) 38 (59.4)	5 (7.8)	21 (32.8)
	<i>12 months</i>	HP (n=66) 13 (19.7)	7 (10.6)	46 (69.7)
		PA (n=64) 8 (12.5)	5 (7.8)	51 (79.7)
EQ-5D-3L	<i>2 weeks</i>	HP (n=66) 42 (63.6)	1 (1.5)	23 (34.9)
		PA (n=64) 40 (62.5)	3 (4.7)	21 (32.8)
	<i>4 weeks</i>	HP (n=66) 41 (62.1)	2 (3.0)	23 (34.9)
		PA (n=64) 42 (65.6)	4 (6.3)	18 (28.1)
	<i>3 months</i>	HP (n=66) 39 (59.1)	2 (3.0)	25 (37.9)
		PA (n=64) 39 (59.1)	5 (7.8)	20 (31.3)
	<i>6 months</i>	HP (n=66) 31 (47.0)	7 (10.6)	28 (42.4)
		PA (n=64) 36 (56.3)	5 (7.8)	23 (35.9)
	<i>12 months</i>	HP (n=66) 13 (19.7)	7 (10.6)	46 (69.7)
		PA (n=64) 8 (12.5)	5 (7.8)	51 (79.7)



Chapter 6

Cost-effectiveness of sigmoid
resection with primary anastomosis
or end colostomy for perforated
diverticulitis: an analysis of the
randomized Ladies trial

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British Journal of Surgery (10 June 2020)

Abstract

Introduction

Several studies have been published favouring sigmoidectomy with primary anastomosis (PA) over the Hartmann's procedure (HP) for perforated diverticulitis with purulent or faecal peritonitis (Hinchey grade III or IV), but cost-related outcomes were scarcely reported. Therefore, the present study aimed to evaluate costs and cost-effectiveness within the DIVA arm of the Ladies trial.

Methods

A cost-effectiveness analysis of the DIVA arm of the multicentre, randomised Ladies trial, comparing PA and HP for Hinchey grade III or IV diverticulitis, was conducted. During 12-month follow-up, resource use, indirect costs (SF-HLQ), and quality of life (EQ-5D) were prospectively collected and analysed according to the modified intention-to-treat principle. Main outcomes were incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR), expressed as the ratio of incremental costs and the incremental probability of being stoma-free or incremental quality-adjusted life-years, respectively.

Results

Overall, 130 patients were included, of which 64 were allocated to PA (Hinchey III/IV: 46/20) and 66 to HP (Hinchey III/IV: 46/18). Overall mean costs per patient were lower for PA (€20 544 (95%CI 19 569 to 21 519) compared to HP (€28 670 (95%CI 26 636 to 30 704)), with a mean difference of €-8 126 (95%CI -14 660 to -1 592). Moreover, an ICER of €-39 094 (95%BCaCI -1 213 to -116) was found, indicating PA to be more cost-effective. The ICUR was €-101 435 (95%BCaCI: -1 113 264 to 251 840).

Conclusion

Primary anastomosis is more cost-effective than a Hartmann's procedure for perforated diverticulitis with purulent or faecal peritonitis.

Introduction

Acute diverticulitis is a common diagnosis in developed countries that is associated with considerable healthcare costs (1-5). The incidence of perforated diverticulitis with purulent or faecal peritonitis (Hinchey grade III or IV) is increasing, thereby emphasizing the need for cost-effective emergency surgical management (6, 7).

In recent years, results have been published favouring sigmoidectomy with primary anastomosis (PA) over Hartmann's procedure (HP) for the treatment of Hinchey III and IV diverticulitis (8). Benefits of PA comprise lower short-term morbidity rates after index and reversal procedures, as well as a higher rate of stoma-free survival, shorter time to stoma reversal and shorter postreversal hospital stay (8-11). Although these outcomes might reduce associated costs, studies comparing the two treatment strategies in terms of related costs and cost-effectiveness are scarce. Therefore, a cost-effectiveness analysis was undertaken comparing PA (with or without defunctioning ileostomy) with HP in patients treated in the DIVA arm of the Ladies trial (11, 12).

Methods

This cost-effectiveness analysis was conducted within the DIVA arm of the Ladies trial. The study protocol, including details of cost analyses and clinical outcomes, has been reported previously (11, 12). In summary, the Ladies trial was an international, multicentre, parallel-group, randomized, open-label superiority trial of the surgical management of perforated diverticulitis. The aim of the DIVA arm was to compare HP and PA (with or without defunctioning ileostomy) as treatment for Hinchey III or IV diverticulitis. After diagnostic laparoscopy, patients were assigned randomly to HP or PA in a 1 : 1 ratio. Patients with dementia, a history of sigmoidectomy or pelvic radiotherapy, chronic steroid treatment (at least 20 mg daily) or preoperative shock requiring inotropic support were excluded. The primary endpoint of the DIVA arm was 12-month stoma-free survival and secondary outcomes (such as morbidity and readmissions) were also recorded. The study was registered at trialregister.nl (NTR2037) and ClinicalTrials.gov (NCT01317485), and designed in accordance with the Declaration of Helsinki and good clinical practice guidelines. The study protocol was approved by the ethical review board, and written informed consent was obtained from all patients before randomization. The CHEERS guideline and checklist (13) were used as guidance for the present cost-effectiveness analysis.

Economic evaluation

The present analysis aimed to assess the cost-effectiveness and cost-utility of HP compared with PA during the first 12 months after the index procedure, and included both direct and indirect costs (medical and non-medical). The economic evaluation was performed from a societal perspective, and in accordance with the guidelines for health economic analyses published by the Dutch National Health Care Institute (14).

Resource use

Data on resource use were collected prospectively through clinical record forms and study questionnaires completed 1, 3, 6, 9 and 12 months after the index procedure. Direct medical costs were those related to index and stoma reversal surgery and related admissions (such as ward and ICU stay), reinterventions (acute relaparotomy or percutaneous drainage), additional diagnostic imaging (X-ray, ultrasound imaging, CT), readmissions, stoma care, emergency department visits, and outpatient consultation visits with the surgeon, gastroenterologist, general practitioner or company physician. Costs of the index procedure actually performed were used and did not include the cost of the study protocol-based diagnostic laparoscopy. Costs associated with home and informal care and travel expenses were considered as direct non-medical costs. Indirect non-medical costs resulting from work absence or decreased productivity were determined by use of the Short Form Health and Labour Questionnaire (SF-HLQ)(15). To estimate loss of productivity, the friction costs method was used with age-adjusted mean daily wages derived from the Dutch National Health Care Institute guideline (14). Total costs per patient were calculated by multiplying resources used by associated unit costs.

Quality-adjusted life-years

Health-related quality of life (QoL) and quality-adjusted life-years (QALYs) were derived from the EuroQol Five Dimensions three-level questionnaire (EQ-5D-3 L™; EuroQol Group, Rotterdam, the Netherlands) at 2 and 4 weeks, 3, 6 and 12 months after the index procedure. Outcomes were scored from 0 to 1 according to the Dutch EQ-5D™ tariff, where 1 is considered to represent optimal QoL.

Unit costs

Unit costs were calculated according to the methods described by Vennix and colleagues (16), and were estimated based on top-down cost calculations from the hospital costs ledger of the Amsterdam University Medical Centre and Dutch guideline on unit costing in healthcare (17). Moreover, bottom-up cost calculations for laparoscopic and open sigmoidectomy with and without PA were performed, including costs of instruments (reusable and disposable), and costs of personnel and overheads per time unit. As the index procedures and Hartmann's reversal procedures could be open or laparoscopic, mean costs were calculated taking the ratio of these different possible procedures into account. Costs were calculated in euros, adjusted to 2018 by the Dutch consumer price index.

Statistical analysis

Depending on data distribution, continuous variables are presented as median (i.q.r.) or mean (s.d.). Categorical variables are shown as numbers with percentages. Patients were analysed according to the modified intention-to-treat principle, with costs calculated based on the index procedure actually performed. The intention-to-treat approach was deemed modified owing to the exclusion of three patients shortly after randomization who were found to have alternative diagnoses (11). The bias-corrected and accelerated (BCa) bootstrapping method (1000 samples) was used to calculate 95 per cent confidence intervals (18). Missing data on EQ-5D™ values and indirect costs were imputed by means

of multiple imputation, taking into account age, sex, Hinchey grade, randomization and direct costs. Imputed data were pooled according to Rubin's rule (19). To determine the robustness of the calculated costs, sensitivity analyses were performed by varying unit costs of resources used (direct medical costs). Incremental cost-effectiveness (ICER) and cost-utility (ICUR) ratios were calculated as the mean difference between treatment groups in total costs per patient divided by the mean difference in probability of being stoma-free and mean difference in QALYs respectively. Cost-effectiveness planes and acceptability curves were derived. Analyses were performed using SPSS® version 24.0 (IBM, Armonk, New York, USA) and R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Between 1 July 2010 and 22 February 2013, and between 9 June 2013 and 6 June 2016, patients could be included in the DIVA arm of the Ladies trial. Trial inclusion was temporarily paused, owing to the early termination of the LOLA arm of the study. Eventually, a total of 130 patients were included according to a modified intention-to-treat principle, of whom 66 were analysed in the HP group and 64 in the PA group. One patient in the PA group was lost to follow-up after 30 days (Fig. S1, supporting information). All patients were included in the present cost evaluation. Baseline and operative characteristics are summarized in Table 1. Full trial details and outcomes have been published previously (11). Response rates to the SF-HLQ questionnaires are documented in Table S1 (supporting information).

Costs and resource use

A summary of unit costs of major resources is provided in Table 2, with full details in Table S2 (supporting information). Resource use and calculated costs are shown in Table 3. Stoma-related costs were significantly higher in the HP group (€8372, 95 per cent c.i. 7316 to 9429) than in the PA group (€4382, 3481 to 5284), with a mean difference of €-3990 (-5370 to -2611). Overall total costs were €1 892 206 for the HP group and €1 314 798 for the PA group. Mean costs per patient were €28 670 (26 636 to 30 704) and €20 544 (19 569 to 21 519) respectively. This amounted to a mean difference in costs of €-8126 (-14 660 to -1592) in favour of PA.

Cost-effectiveness and cost-utility

The mean probability of being stoma-free at end of the 12-month follow-up was 86 (95 per cent c.i. 74 to 93) per cent for the PA group and 65 (53 to 75) for the HP group, with a significant mean difference of 21 (7 to 36) per cent. Fig. 1 shows a cost-effectiveness plane, indicating the relationship between incremental costs and the incremental probability of being stoma-free and alive. The ICER was €-39 094 (95 per cent BCa c.i. -1213 to -116), indicating that PA was more cost-effective than HP. The associated willingness-to-pay curve is shown in Fig. S2 (supporting information).

The mean value of QALYs during the 12-month follow-up was 0.72 (95 per cent c.i. 0.69 to 0.76) in the PA group, compared with 0.64 (0.60 to 0.68) in the HP group.

The mean difference in QALYs was 0.08 (−0.03 to 0.19), which was not statistically significant. The ICUR was €−101 435 (95 per cent BCa c.i. −1 113 264 to 251 840). A cost–utility plane and willingness-to-pay curve are shown in Fig. 2 and Fig. S3 (supporting information) respectively.

Sensitivity analyses

Table 4 shows the results of sensitivity analyses, in which unit costs for specified cost groups were increased and decreased by 20 or 50 per cent, while those for other cost groups were not changed. Overall, these results demonstrated that PA was associated with lower costs, with cost differences ranging from €−7263 to €−8932.

Discussion

Admission rates for diverticulitis have increased over the past few decades (6, 20–23) and the incidence of perforated disease, for which surgery is often needed, has risen (24–26). In a retrospective study (27), overall expenses were between 74 and 229 per cent higher for HP than PA. More recently (28), in-hospital costs within an RCT were found to be higher for HP, but this was not statistically significant. The present study differed from previous analyses by capturing all costs prospectively, including indirect non-medical and other resource expenses (such as those related to readmissions or outpatient department visits) over the full 12-month follow-up. It showed that PA was more cost-effective in the first postoperative year and in terms of the probability of being stoma-free. Advantages of PA derive from a shorter time to, and less morbidity after, stoma reversal, and a shorter hospital stay, which are likely to reduce costs (11). Indeed, a large difference in absolute stoma-related costs was identified in favour of PA. This is in line with a cost-effectiveness analysis of the LOLA arm of the Ladies trial (16), in which stoma-related costs were higher for resection than laparoscopic lavage for Hinchey III diverticulitis, and the economic analysis of the related DILALA (DIverticulitis – LAParoscopic LAVage versus resection (Hartmann’s procedure) for acute diverticulitis with peritonitis) study (29).

In terms of generalizability, some aspects are of importance to consider when interpreting the present outcomes. The majority of patients included in the Ladies trial were Dutch (11), and unit costs and subsequent calculations are based on that healthcare system. The results should be interpreted within the context of the inclusion and exclusion criteria that applied to the DIVA arm. Therefore, strictly speaking, the present outcomes apply only to haemodynamically stable, immunocompetent patients aged less than 85 years (11). Enrolment was terminated early because of slow accrual. Although not uncommon for RCTs in the emergency setting (30), early termination may limit the sample size and statistical power. The study was not specifically powered to show differences in cost-associated or patient-reported outcomes. Hence, it was decided not to differentiate between Hinchey III and IV diverticulitis in the present study, as this would have further reduced group sizes. In spite of the sample size, significant differences in overall mean costs per patient were identified, and their robustness was demonstrated in sensitivity analyses. Another limitation was the response rate to the questionnaires sent out during

follow-up, which ranged from 47 to 64 per cent. Multiple imputation techniques were used to handle missing data and to decrease the influence of potential attrition bias.

This study has several strengths, including the setting of a multicentre randomized trial with cost data collected prospectively from a societal perspective, and indirect non-medical costs (such as absence from work and productivity losses) taken into account. These factors are relevant to consider as the disease is increasingly being seen in younger patients of working age (20, 21, 23). The assessment of unit costs came from the hospital ledger and Dutch costing manual (14), rather than being derived from diagnosis-related group data, to better reflect clinical practice at a more individual level.

In general, the treatment of diverticulitis has shifted towards less aggressive approaches, which might also have beneficial effects on associated costs (31). The avoidance of antibiotics for uncomplicated diverticulitis has been proven to be safe in both the short and long term (32-35). The role of percutaneous drainage for diverticulitis with abscess formation has been debated (36, 37). Subsequently, follow-up without elective colectomy after non-operative treatment of an initial episode of diverticulitis with abscess formation or local extraluminal air seems justified (38, 39). Moreover, evidence shows that HP for perforated diverticulitis should be avoided if possible and that PA is preferred (9-11). The present cost-effectiveness analysis has provided a health economic argument for use of PA over HP for perforated diverticulitis.

Acknowledgements

The authors thank all patients who were willing to participate in this trial, and the collaborators in the DIVA arm of the Ladies trial. The Ladies trial is part of a national consortium: the Dutch Diverticular Disease (3D) Collaborative Study group. The Ladies trial was funded by a grant from the Netherlands Organization for Health Research and Development (ZonMw 171002213).

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Tables

Table 1 Summary of baseline and operative characteristics

	Hartmann's procedure (n=66)	Primary anastomosis (n=64)
Patient characteristics		
Age (years)	61.7 (11.4)	62.4 (13.1)
Sex (F/M)	25/41 (38/62)	23/41 (36/64)
BMI (kg/m ²)	28 (4.7)	26.3 (4.8)
ASA score*		
I-II	37 (63)	45 (76)
III-IV	22 (37)	14 (24)
Hinchey grade IV	20 (30)	18 (28)
Operative characteristics		
Laparoscopic lavage	0	1 (1.6)
Hartmann's procedure	65 (98)	7 (10.9)
Primary anastomosis	1 (2)	56 (87.5)
Without stoma	1 (2)	18 (28.1)
With stoma	65 (98)	46 (71.9)
Duration of surgery (minutes)	118 (95.5-135.3)	125 (110.0-154.0)
Laparoscopic procedure	20 (30)	17 (27)

Data are n (%), mean (SD), median (IQR). ASA = American Society of Anesthesiologists score, BMI = body mass index. *Missing in seven patients in the Hartmann's procedure group and five patients in the primary anastomosis group.

Table 2 Major resources and unit costs

	Costs (€)	Unit
Hartmann's procedure	3 247	Procedure
Primary anastomosis	3 914	Procedure
Laparoscopic lavage	2 346	Procedure
Ileostomy reversal	2 655	Procedure
Colostomy reversal	4 087	Procedure
Acute relaparotomy	3 476	Procedure
Percutaneous drainage	174	Procedure
Elective sigmoid resection	4 266	Procedure
Incisional hernia repair	1 305	Procedure
Surgical ward stay	419	Day
Intensive care unit stay	2 084	Day

Values are mean costs in €, as indexed for 2018.

Table 3 Resource use and costs

		Hartmann's procedure (n=66)		Primary anastomosis (n=64)	
	Unit	Total units	Total costs (€)	Total units	Total costs (€)
Index admission					
Hartmann's procedure	Procedure	65	211 083	7	22 732
Primary anastomosis	Procedure	1	3 914	56	219 181
Laparoscopic lavage	Procedure	0	0	1	2 346
Surgical ward	Day	733	307 076	591	247 588
Intensive care unit	Day	197	410 611	87	181 336
Additional imaging	Test	264	31 039	159	21 448
Subtotal			963 723		694 630
Mean subtotal per patient (95% CI)		14 602 (8 514 to 20 689)		10 854 (9 126 to 12 581)	
Mean difference in subtotal (95% CI)			-3 748 (-10 101 to 2 604)		
Readmissions and reinterventions					
Acute reinterventions	Procedure	18	31 064	12	28 154
Elective reinterventions	Procedure	4	5 218	1	1 305
Readmission surgical ward	Day	172	72 056	142	59 488
Readmission intensive care unit	Day	0	0	0	0
Subtotal			108 339		88 946
Mean subtotal per patient (95% CI)		1 641 (626 to 2 657)		1 390 (677 to 2 102)	
Mean difference in subtotal (95% CI)			-252 (-1 488 to 984)		
Stoma-related costs					
Stoma care	Day	13 118	245 965	8288	104 737
Reversal surgery	Procedure	45	183 915	38	106 612
Reversal admission (surgical ward + intensive care unit)	Day	277	122 705	165	69 123
Subtotal			552 584		280 473
Mean subtotal per patient (95% CI)		8 372 (7 316 to 9 429)		4 382 (3 481 to 5 284)	
Mean difference in subtotal (95% CI)			-3 990 (-5 370 to -2 611)		
Other costs					
Imaging	Test	64	9 282	38	4 811
Consultations and travel expenses	Visit	349	30 038	295	26 423
Total direct medical costs			1 663 966		1 095 283
Indirect non-medical costs			228 240		219 515
Total costs (12 months)			1 892 206		1 314 798
Mean costs per patient (95% CI)			28 670 (26 636 to 30 704)		20 544 (19 569 to 21 519)
Mean difference in costs (95% CI)			-8 126 (-14 660 to -1 592)		

Values in parentheses are 95% confidence intervals. Smaller cost groups (e.g. hospital and general practitioner visits) are not shown, but are included in (sub)total costs.

Table 4 Sensitivity analyses of medical costs

	Hartmann's procedure (€)	Primary anastomosis (€)	Cost difference (€)
Total medical costs	25 212	17 114	-8 098
(base analysis)	(21 251 to 34 132)	(15 297 to 19 636)	(-17 016 to -3 550)
Index surgery			
-50%	23 583	15,206	-8 377
	(19 603 to 32 482)	(13 398 to 17 789)	(-17 214 to -3 818)
+50%	26 840	19 022	-7 818
	(22 847 to 37 381)	(16 978 to 21 455)	(-18 129 to -3 269)
Hospital stay (ward, intensive care unit)			
-20%	23 036	15 773	-7 263
	(19 258 to 30 896)	(14 139 to 17 939)	(-14 878 to -2 910)
+20%	27 386	18 454	-8 932
	(22 398 to 39 156)	(16 284 to 21 358)	(-19 534 to -3 261)
Stoma-associated costs			
-20%	23 537	16 237	-7 300
	(19 566 to 33 672)	(14 598 to 18 812)	(-16 843 to -2 507)
+20%	26 886	17 990	-8 896
	(22 880 to 35 540)	(16 064 to 20 586)	(-17 734 to -4 320)
Acute or elective reintervention			
-20%	25 102	17 022	-8 079
	(21 174 to 35 659)	(15 370 to 19 443)	(-18 375 to -3 742)
+20%	25 321	17 206	-8 116
	(21 399 to 36 105)	(15 499 to 19 746)	(-18 526 to -3 742)

Figures

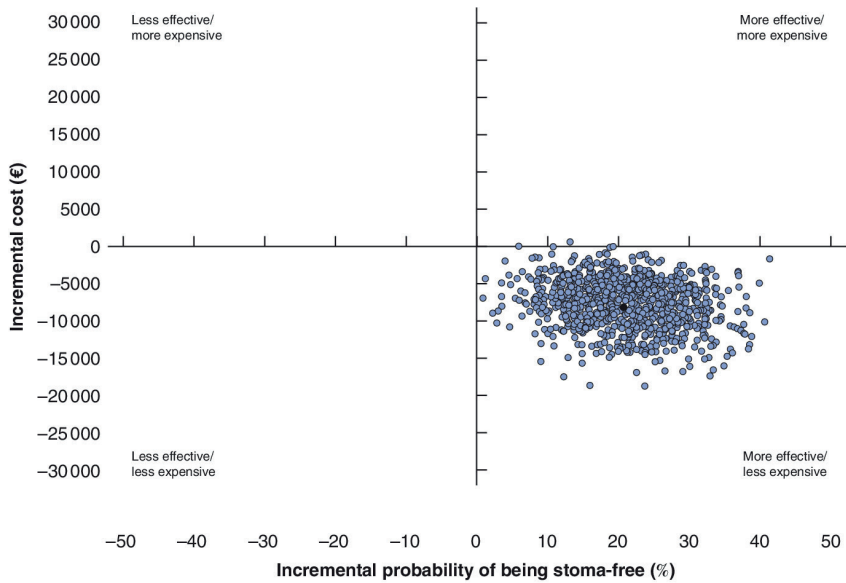


Figure 1 Cost-effectiveness plane
Black dot indicates the point estimate upon which the 1000 bootstrap samples are based.

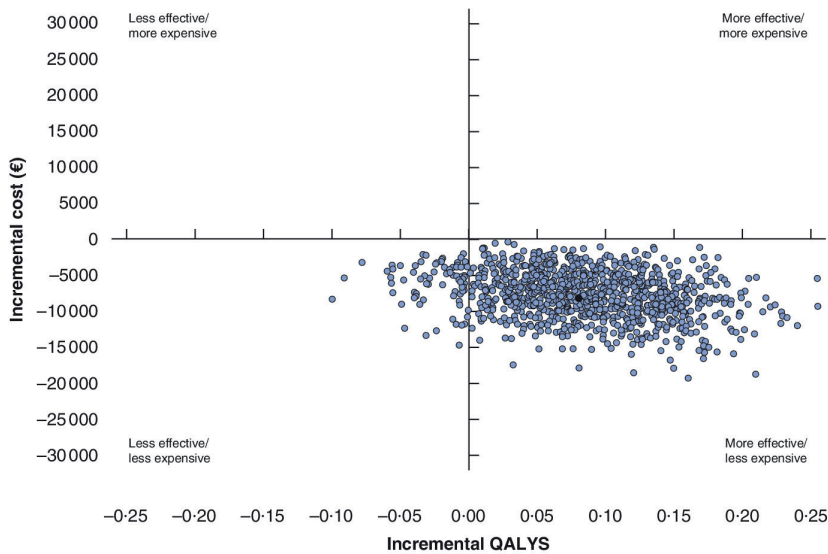


Figure 2 Cost-utility plane
Black dot indicates the point estimate upon which the 1000 bootstrap samples are based. QALY, quality-adjusted life-year.

Supporting information

Table S1 Health and labour questionnaire response rates

Time point	Group	Observed	Died	Missing
1 month	HP (n=66)	41 (62.1)	2 (3.0)	23 (34.8)
	PA (n=64)	41 (64.1)	4 (6.3)	19 (29.7)
3 months	HP (n=66)	39 (59.1)	2 (3.0)	25 (37.9)
	PA (n=64)	40 (62.5)	5 (7.8)	19 (29.7)
6 months	HP (n=66)	31 (47)	7 (10.6)	28 (42.4)
	PA (n=64)	38 (59.4)	5 (7.8)	21 (32.8)
9 months	HP (n=66)	31 (47)	7 (10.6)	28 (42.4)
	PA (n=64)	36 (56.3)	5 (7.8)	23 (35.9)
12 months	HP (n=66)	34 (51.5)	7 (10.6)	25 (37.9)
	PA (n=64)	35 (54.7)	5 (7.8)	24 (37.5)

Data are presented as n (%).

Table S2 Unit costs

	Unit	Costs (€)	Valuation method/source	Unit source
Index procedure				
Hartmann's procedure	Procedure	3 247	Hospital ledger*/bottom-up	CRF
Primary anastomosis	Procedure	3 914	Hospital ledger/bottom-up	CRF
Laparoscopic lavage	Procedure	2 346	Hospital ledger/bottom-up	CRF
Admission				
Surgical ward	Day	419	Dutch costing manual	CRF
Intensive care	Day	2 084	Dutch costing manual	CRF
Stoma reversal				
Ileostomy reversal	Procedure	2 655	Hospital ledger/top-down	CRF
Colostomy reversal	Procedure	4 087	Hospital ledger/top-down	CRF
Acute reintervention				
Percutaneous drainage	Procedure	174	Hospital ledger/top-down	CRF
Relaparotomy	Procedure	3 476	Hospital ledger/top-down	CRF
Elective reintervention				
Sigmoid resection	Procedure	4 266	Hospital ledger/top-down	CRF
Incisional hernia repair	Procedure	1 305	Hospital ledger/top-down	CRF
Stoma revision	Procedure	1 690	Hospital ledger/top-down	CRF
Diagnostic procedures				
Chest/abdominal X-ray	Procedure	71	Hospital ledger/top-down	CRF
CT abdomen	Procedure	203	Hospital ledger/top-down	CRF
Ultrasonography abdomen	Procedure	153	Hospital ledger/top-down	CRF
Consultations				
Emergency care	Visit	268	Dutch costing manual	Patient-reported
General practitioner	Visit	34	Dutch costing manual	Patient-reported
Company physician	Visit	34	Dutch costing manual	Patient-reported
Medical specialist	Visit	76	Dutch costing manual	Patient-reported
Stoma care				
Ileostomy materials	Day	16	Supplier/health insurance	CRF
Colostomy materials	Day	19	Supplier/health insurance	CRF
Stoma nurse visits	Year	66	Dutch costing manual	CRF
Home care				
Nursing	Hour	52	Dutch costing manual	Patient-reported
Informal care	Hour	14	Dutch costing manual	Patient-reported
Travel expenses				
General practitioner visit	Visit	4	Dutch costing manual	Patient-reported
Hospital visit	Visit	6	Dutch costing manual	Patient-reported
Indirect non-medical costs	Hour	36	Dutch costing manual	Patient-reported

Values are mean costs in €, as indexed for 2018. CRF, case record form; GP, general practitioner. *Hospital ledger: hospital ledger of 2012 from the University Medical Center Amsterdam (AMC), Amsterdam, The Netherlands.

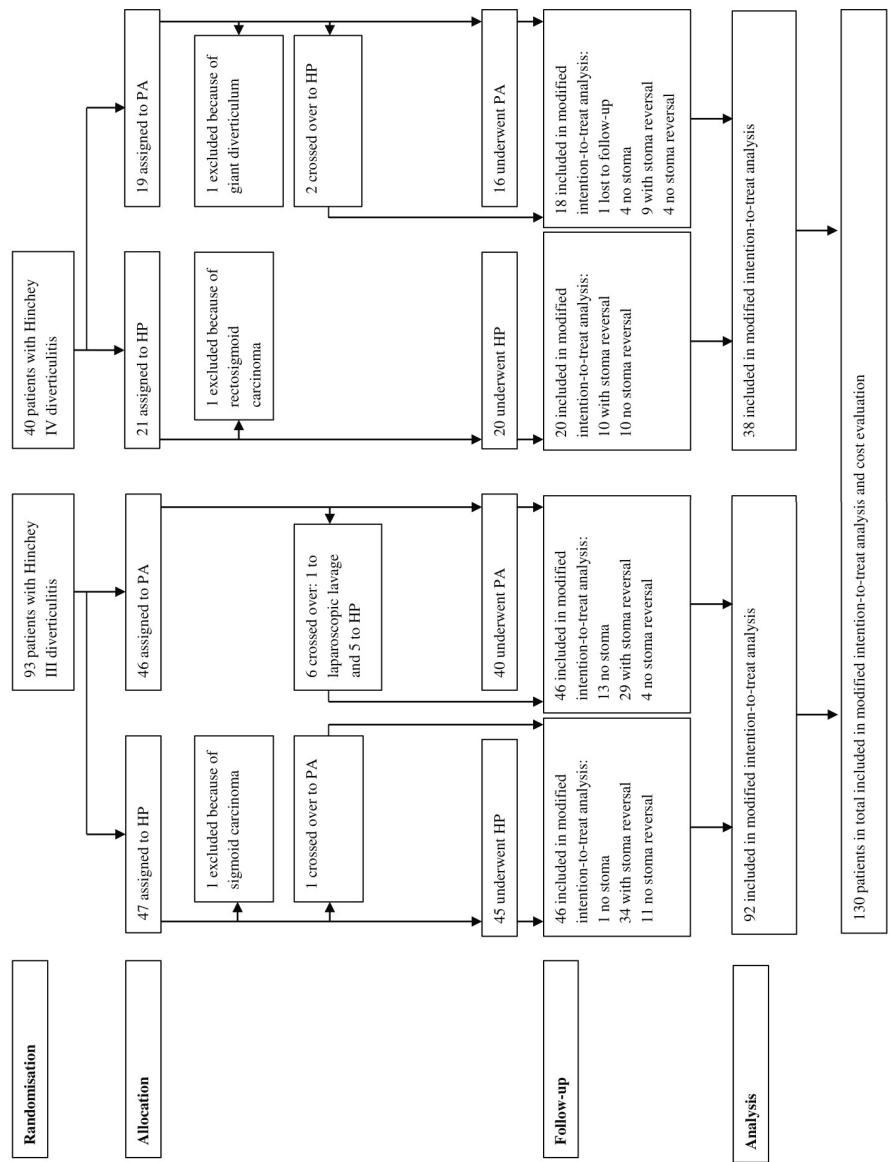


Figure S1 Flow chart

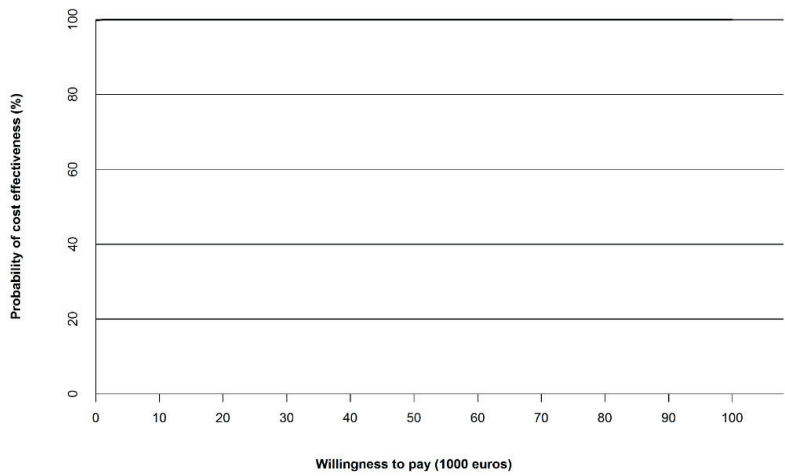


Figure S2 Willingness-to-pay in relation to probability of cost-effectiveness

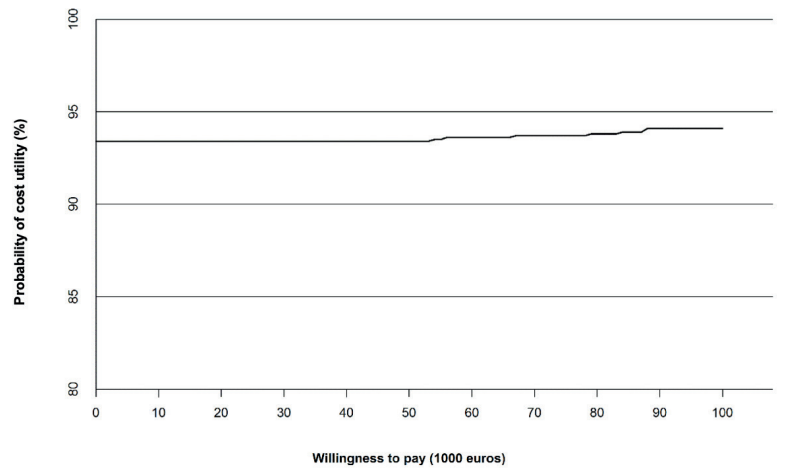
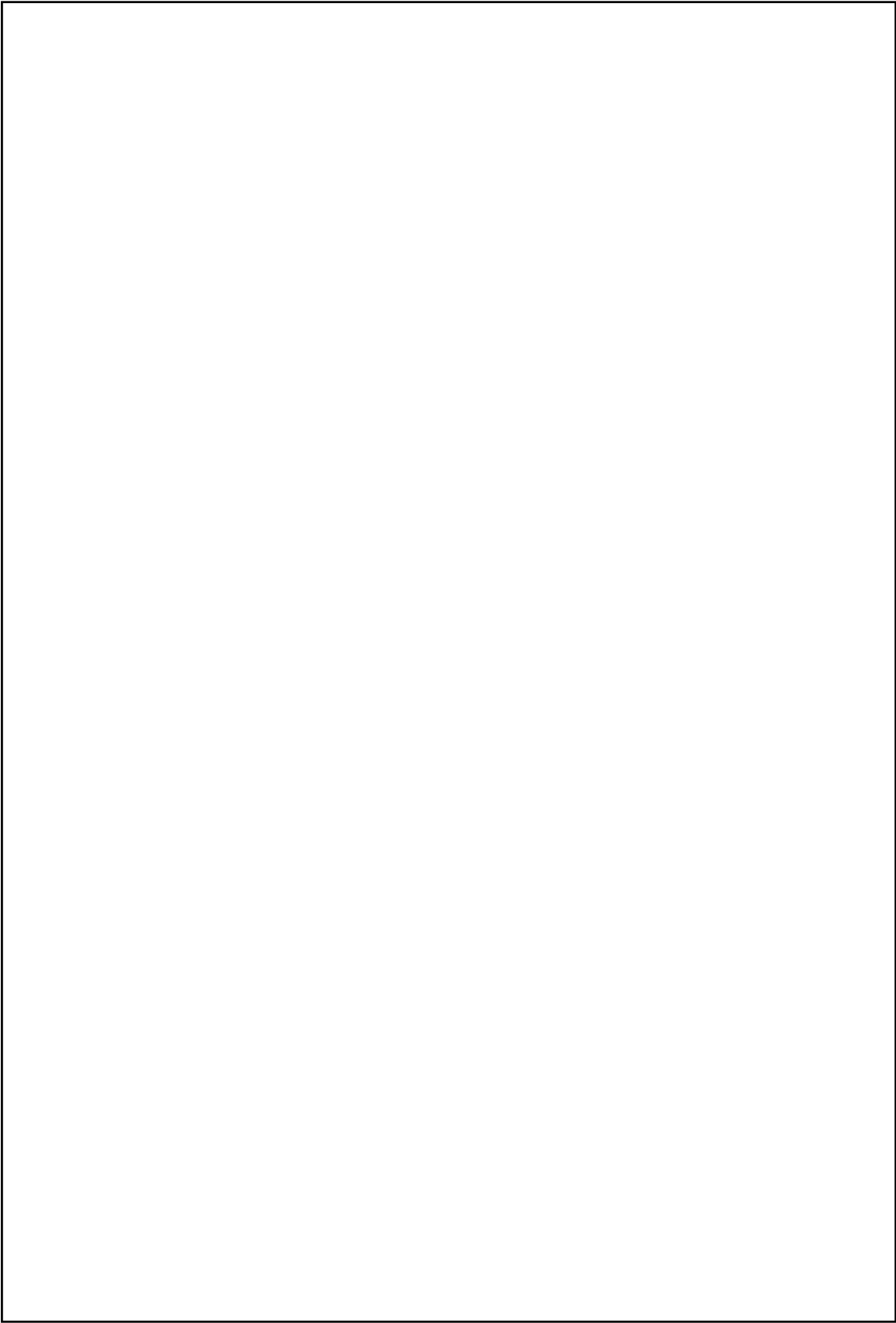


Figure S3 Willingness-to-pay in relation to probability of cost-utility



Chapter 7

Sigmoid resection with primary anastomosis versus the Hartmann's procedure for perforated diverticulitis with purulent or fecal peritonitis: a systematic review and meta-analysis

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International Journal of Colorectal Disease (5 June 2020)

Abstract

Background

The optimal surgical approach for perforated diverticulitis with purulent or fecal peritonitis (Hinchey grade III or IV) remains debated. In recent years, accumulating evidence comparing sigmoid resection with primary anastomosis (PA) with the Hartmann's procedure (HP) was presented. Therefore, the aim was to provide an updated and extensive synthesis of the available evidence.

Methods

A systematic search in Embase, MEDLINE, Cochrane, and Web of Science databases was performed. Studies comparing PA to HP for adult patients with Hinchey III or IV diverticulitis were included. Data on mortality, morbidity, stoma reversal, patient-reported and cost-related outcomes were extracted. Random-effects models were used to pool data and estimate odds ratios (OR).

Results

From a total of 1560 articles, four randomized controlled trials and ten observational studies were identified, reporting on 1066 Hinchey III/IV patients. Based on trial outcomes, PA was found to be favorable over HP in terms of stoma reversal rates (OR 2.62, 95%CI 1.29, 5.31) and reversal-related morbidity (OR 0.33, 95%CI 0.16, 0.69). No differences in mortality (OR 0.83, 95%CI 0.32, 2.19), morbidity (OR 0.99, 95%CI 0.65, 1.51) and reintervention rates (OR 0.90, 95%CI 0.39, 2.11) after the index procedure were demonstrated. Data on patient-reported and cost-related outcomes were scarce, as well as outcomes in PA patients with or without ileostomy construction and Hinchey IV patients.

Conclusions

Although between-study heterogeneity needs to be taken into account, the present results indicate that primary anastomosis seems to be the preferred option over Hartmann's procedure in selected patients with Hinchey III or IV diverticulitis.

Introduction

Up to 35% of patients with acute diverticulitis present with complicated disease, such as perforation with purulent or fecal peritonitis (Hinchey III or IV)(1-4). Treatment of perforated diverticulitis with peritonitis generally requires emergency surgical treatment (5). However, the optimal surgical treatment strategy remains a topic of debate.

Although the Hartmann's procedure (HP) has been the favored approach for most surgeons, outcomes of sigmoidectomy with primary anastomosis (PA) have been reported to be comparable to those of HP (6, 7). Previous studies have found PA to be associated with higher stoma reversal rates and another important potential benefit of PA is the option to avoid a defunctioning ileostomy in selected cases (8-11). Moreover, restoration of intestinal continuity after HP is reported to be associated with higher morbidity and mortality rates (12, 13). Hence, PA has the potential benefit to decrease patient burden, lower associated healthcare costs, and improve patient-reported outcomes (14).

Particularly in the light of increased incidence and admission rates of perforated diverticulitis, a critical appraisal of treatment strategies and their outcomes is an important step towards consensus on its optimal surgical approach (15). Therefore, the aim of this systematic review and meta-analysis was to assess outcomes of HP and PA (with or without ileostomy) for perforated diverticulitis with purulent or fecal peritonitis.

Materials and methods

The study was conducted following the MOOSE and PRISMA guidelines (16, 17) and was registered in PROSPERO (CRD42019135333). Approval of the institutional review board and written consent were not required.

Study design

Case reports, review articles, meta-analyses, letters, abstracts or comments were excluded. Randomized controlled trials (RCTs) and prospective or retrospective cohort studies were included if they met the following criteria: reporting on (1) patients ≥ 18 years of age with acute left-sided perforated diverticulitis with peritonitis (Hinchey III or IV) and (2) a comparison of HP and PA (with or without defunctioning ileostomy). Exclusion criteria were: (1) studies reporting on Hinchey I or II diverticulitis, chronic diverticular complications (e.g. fistulae or obstruction), non-diverticular colorectal disease, or elective surgery, in which outcomes could not be assessed separately from Hinchey III and IV diverticulitis, (2) non-comparative studies, and (3) non-English studies.

Systematic literature search

A biomedical information specialist performed a systematic search in collaboration with one of the authors (DL). The Embase, MEDLINE, Cochrane, and Web of Science databases were searched on June 17, 2019. Publication date was not limited and the initial search was not restricted by language. Search syntaxes and results per database

are given in the Appendix. An additional search through reference lists was performed. Two researchers (DL and PE) independently reviewed the identified articles by title and abstract and, subsequently, by full-text using EndNote X9®. Differences in article selection were discussed and articles were in- or excluded after consensus was reached between reviewers.

Data collection

Two researchers (DL and PE) extracted data, which were checked by a third independent researcher (RB). Discrepancies were discussed until consensus was reached. In case of uncertainties with regard to reported outcomes, corresponding authors were contacted when possible. The following study details were collected: author, year, country/countries, design, and length of follow-up, and -if applicable- sample size, inclusion period, number of screened and included patients, eligibility criteria, cross-overs, moment of randomization, primary endpoint, and trial accrual. Extracted baseline patient and operative characteristics were: sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, preoperative disease severity, Hinchey grade, previous diverticulitis and abdominal surgery, surgical expertise, time and duration of surgery, blood loss, approach (open/laparoscopic), anastomotic configuration and construction, drain placement and intraoperative lavage. Moreover, the following outcomes were collected: mortality, morbidity, hospital stay, intensive care unit (ICU) stay, (ongoing) sepsis, anastomotic leakage, intra-abdominal abscess occurrence and drainage, malignancies, surgical site infections (SSI), organ dysfunction, fascial dehiscence, stoma reversal rates, and hernia rates. Additionally, data on patient-reported outcomes and associated costs were extracted.

Risk of bias and quality assessment

Study quality was assessed independently by two researchers (DL and PE) using the level of evidence (18), Newcastle-Ottawa Scale (NOS), and Methodological Index for Non-Randomized Studies (MINORS) criteria (19, 20). For RCTs, the Cochrane Collaboration's risk-of-bias tool was used(21). Discrepancies in quality assessment outcomes were resolved by discussion.

Data synthesis and statistical analysis

To calculate pooled odds ratios (OR) with 95%CI, the Mantel-Haenszel random-effects model was used, which takes between-study and within-study variance into account. For continuous variables, inverse variance weighted random-effects models were used to calculate mean differences (MD) with 95%CI. Statistical heterogeneity was evaluated by calculating Q statistics and I^2 . In addition, risk differences (RD), risk ratios (RR), and numbers needed to treat (NNT) were calculated for outcomes that were significantly different between treatment groups. Analyses were performed using RevMan 5.3 (Cochrane Centre, Copenhagen, Denmark).

Results

Systematic literature search

Details of the study selection are provided in a PRISMA flow diagram (Fig. 1). After duplicate removal, 1560 of 2578 articles were further assessed. Eventually, 14 articles were included after title and abstract screening and full-text reading.

Study, patient and operative characteristics

Study characteristics are given in Table 1. Overall, four RCTs were included (22-25), as well as three prospective (26-28) and seven retrospective observational studies (29-35). Overall, data on a total of 1274 patients were available most of whom had Hinchey grade III/IV diverticulitis (1066/1274, 83.7%). Data were available on 731 and 536 patients who underwent or were allocated to HP or PA, respectively. Risk of bias assessment of the included RCTs is shown in Supplemental Fig. 1. For the non-randomized studies, the NOS and MINORS scores ranged between 6–9 and 13–18, respectively. An overview of patient baseline characteristics is given in Table 2. Moreover, Supplemental Tables 1 and 2 provide details on the reported operative characteristics of index and reversal procedures. In Supplemental Table 3, summarized results of a quantitative analysis of baseline characteristics in the included observational studies are presented. As compared to HP, PA patients were more likely to undergo surgery for Hinchey III diverticulitis (OR 2.45, 95% CI 1.30, 4.63, $p=0.006$) and to have a lower mean age (MD -4.84, 95% CI -9.41, -0.27, $p=0.04$) and MPI score (MD -3.58, 95% CI -5.70, -1.47, $p=0.0009$).

Randomized controlled trials

Details of the four included RCTs are provided in Supplemental Table 4. Overall, 204 HP and 180 PA patients were analyzed. Reported in- and exclusion criteria varied between trials, mainly in terms of exclusion criteria. The only trial to report reasons for not screening patients for eligibility and non-inclusion of screened patients was that by Oberkofler and colleagues (23). Overall, 53 patients were not assessed for participation due to disagreement of the surgeon (40% HP, 30% PA with diverting ileostomy, 22% PA without diverting ileostomy, 8% others). Moreover, the authors reported that 21 patients were not included, because they declined to participate ($n=7$) or did not meet inclusion criteria ($n=14$). The Ladies trial(25) was the only study to be able to assess differences between the included patients and a cohort of 235 non-included but eligible patients, showing that in the latter group a GI surgeon was less often present (68.7% vs. 88.5%, $p<0.001$) and the median interval to surgery was longer (13.5 hours (6-43.8) vs. 8.8 (5.3-29.3), $p=0.02$). However, no difference in in-hospital mortality was found for non-included (20/235, 8.5%) and included patients (6/130 (4.6%), $p=0.21$). Three of the four trials randomized preoperatively, whereas in the Ladies trial patients were randomized intraoperatively. All trials were terminated early due to recruitment difficulties. Oberkofler *et al.* (23) reported significant differences in relevant secondary endpoints to be an additional argument for early discontinuation, although they did not specify which endpoints. In total, 31.5% (384/1218) of the overall calculated sample sizes was reached.

Index procedure: mortality

An overview of outcomes after the index procedure is given in Tables 3 and 4. Eleven of the included studies reported on mortality rates during follow-up for Hinchey III/IV patients. As shown in Fig. 2a, no difference was found in the occurrence of short-term mortality in a quantitative analysis of RCTs, with mortality occurring in 5% (9/180) of PA and 6.4% (13/204) of HP patients (OR 0.83 (95% CI 0.32, 2.19)). In addition, long-term mortality, defined as occurring within the trials' full study period, showed no difference between PA and HP (9/179 (5%) vs. 17/204 (8.3%)), OR 0.61, 95% CI 0.25, 1.47) as shown in Fig. 2b. A separate quantitative analysis of data from observational studies ($n = 7$) showed a significant difference in overall mortality in favor of PA (18/146 (12.3%)) as compared to HP (68/233 (29.2%)) with an OR of 0.39 (95% CI 0.18, 0.85) (Fig. 2c).

Index procedure: morbidity

The overall morbidity rates in RCTs are provided in Fig. 3a, which shows no difference between both procedures with an OR of 0.99 (95% CI 0.65, 1.51; PA 91/180 (50.6%) vs. HP 101/204 (49.5%)). An additional analysis of short-term serious complications (Clavien-Dindo grade > IIIa) within the RCTs (Fig. 3b) also did not show a difference between PA and HP (30/145 (20.7%) vs. 31/148 (20.9%)), OR 0.95, 95% CI 0.53, 1.72). Additionally, morbidity could be assessed in four observational studies (Fig. 3c), which showed an OR of 1.01 (95% CI 0.21, 4.96; PA 28/62 (45.2%) vs. HP 85/176 (48.3%)).

Reintervention rates after the index procedure, including surgical reinterventions and abscess drainage, were assessed within the RCTs (Supplemental Fig. 2a) and no differences were demonstrated between both procedures (PA 11/148 (7.4%) vs. HP 13/174 (7.5%); OR 0.90, 95% CI 0.39, 2.11). A separate analysis of reoperation rates within these trial data also showed no differences (Supplemental Fig. 2b). From observational studies ($n = 3$), reintervention rates were 6.7% (6/90) and 16.3% (16/98) for PA and HP, respectively (OR 0.52, 95% CI 0.19, 1.46; see Supplemental Fig. 2c).

Nine studies provided anastomotic leakage rates after the index procedure, which showed the occurrence of 14 leakages in 226 PA patients (6.2%) and 3 leakages in 298 HP patients (1%). In the latter group, one patient had a rectal stump leakage (22), whereas two other patients were stated to have anastomotic leakage due to the presence of fistulas in the study by Regenet et al. [10]. Forest plots of surgical site infections, postoperative (ongoing) sepsis, and fascial dehiscence did not show significant differences between both treatment groups in experimental and observational studies (Supplemental Fig. 3a, b, c, d, e, and f).

Stoma- and reversal-related outcomes

An overview of outcomes after the reversal procedure is given in Supplemental Tables 6a and b. In Fig. 4a, reversal rates of constructed stomas were assessed within the included trials, showing a significant difference in favor of PA (118/147 (80.3%)) over HP (126/203 (62.1%); OR 2.62, 95% CI 1.29, 5.31), with an associated NNT of 5 (Supplemental Table 5). From the assessment of the number of stoma-free patients

during trial follow-up, as provided in Fig. 4b, PA also showed favorable outcomes over HP (PA 150/179 (83.8%) vs. HP 127/204 (62.3%); OR 3.21, 95% CI 1.42, 7.26; NNT 5). Reversal rates of the studies that could not be included are shown in Supplemental Table 6a.

Reasons for non-reversal were mentioned in the trial of Oberkofler *et al.*(23), including patient's choice and the surgeon's risk assessment, but related percentages were not presented. Bridoux and colleagues found that reasons for not undergoing stoma reversal in the HP group were patient's choice (n=8/17) or if a patient was deemed unfit for surgery (n=9/17)(24). The latter was also the case in 2 of 16 PA patients, whereas the other 14 patients had no stoma constructed. In the Ladies trial, reasons were the surgeon's disapproval (HP: n=3/21, PA: n=1/8), patient's preferences (HP: n=2/21, PA: n=1/8), mortality before reversal (HP: 7/21, PA: n=4/8), or they were unknown (HP: n=8/21, PA: n=2/8)(25).

One case of reversal-related mortality was reported within the included studies, which was caused by mesenteric ischemia after atrial fibrillation (24). Postoperative morbidity related to the reversal procedure was assessed in four studies (Fig. 4c), being the four included trials, which showed a significant difference in favor of PA (PA 14/118 (11.9%) vs. HP 34/126 (27%); OR 0.33, 95% CI 0.16, 0.69; NNT 7). This difference was not found when serious complications were assessed in two of the four trials that reported these figures, as shown in Fig. 4d (PA 1/58 (1.7%) vs. HP 6/48 (12.5%); OR 0.18, 95% CI 0.03, 1.15).

Outcomes of index and reversal procedure combined

An analysis of the short-term mortality of the index and reversal procedures combined (Supplemental Fig. 4a) did not show a significant difference, with an OR of 0.76 (PA 9/179 (5%) vs. HP 14/204 (6.9%); 95% CI 0.29, 1.96). Additionally, short-term morbidity was assessed for the combined procedures (Supplemental Fig. 4b), which showed no difference between both treatment groups (PA 88/179 (49.2%) vs. HP 120/204 (58.8%); OR 0.64, 95% CI 0.37, 1.13). The occurrence of anastomotic leakage after both the index and reversal procedure combined was assessed in the four RCTs, which did not show a difference between PA and HP (respectively, 6/179 (3.4%) vs. 6/204 (2.9%); OR 1.04, 95% CI 0.30, 3.52; see Supplemental Fig. 4c).

Outcomes in Hinchey IV patients

Four studies specifically reported on outcomes of Hinchey IV diverticulitis. Binda *et al.*(22) found the type of peritonitis (purulent or fecal) to be significantly related to morbidity (28/75 (37.3%) vs. 10/15 (66.7%), $p=0.047$) and mortality (3/75 (4%) vs. 4/15 (26.7%), $p=0.014$) in multivariate analysis. Outcomes of Hinchey III and IV patients were assessed separately in the Ladies trial(25), showing the 12-month stoma-free survival after PA to be significantly better for both Hinchey grades (III: hazard ratio 2.35, 95%CI 1.49, 3.71; IV: hazard ratio 4.15, 95%CI 1.71, 10.1). Within the Hinchey IV group, no significant differences in short-term postoperative outcomes after the index procedure were demonstrated between HP and PA (mortality: 2/20 (10%) vs. 3/18 (16.7%); overall morbidity: 12/20 (60%) vs. 8/18 (44.4%), $p=0.52$). Also, no

differences in short-term post-reversal outcomes were found, with no mortality in both treatment groups and an overall morbidity of 30% in the HP group and 0% in the PA group ($p=0.21$). Trenti and colleagues(28) performed a logistic regression analysis with Hinchey grade (IV vs. III), Peritonitis Severity Score (≤ 9), ASA (III-IV vs. I-II), and treatment (HP vs. PA), but did not find Hinchey grade to be independently associated with post-operative mortality and morbidity, wound infection, or reoperation. Moreover, in the study by Vermeulen *et al.* (32), multivariate analyses adjusting for treatment, age, ASA, MPI, surgeon's experience, and Hinchey grades showed Hinchey grade IV disease to be independently associated with the outcome as compared to the reference group of Hinchey I patients (postoperative mortality: OR 3.9, 95%CI 1.0, 13.8, $p=0.03$; reinterventions: OR 3.9, 95%CI 1.3, 12.7, $p=0.02$).

Outcomes of primary anastomosis with or without ileostomy

Bridoux *et al.* (24) stated that no related mortality was found in the subgroup of selected PA patients without an ileostomy ($n=15$). Moreover, they reported overall morbidity and serious complication rates to be lower in PA patients without a stoma (respectively, 0% vs. 27%, $p=0.01$, and 23% vs. 67%, $p=0.042$). In the Ladies trial (25), PA patients with ($n=40$) and without ($n=17$) an ileostomy were compared. No differences in overall morbidity (4/17 (23.5%) vs. 18/40 (45%), $p=0.15$) and mortality (0 vs. 3/40 (7.5%), $p=0.55$) were found, but patients without an ileostomy had a significantly shorter median postoperative stay (7 (11-14) days vs. 11 (7-14), $p=0.01$). In their overall cohort (including Hinchey I/II diverticulitis), Vermeulen and colleagues (32) found no difference in complication rates between PA patients with or without an ileostomy (respectively, 19% vs. 11%, $p=0.42$).

Patient-reported outcomes

Patient-reported outcomes were only identified within the Ladies trial(25). During the 12-month follow-up period, questionnaires to measure health-related quality of life were sent out at weeks two and four, and months three, six, and twelve after the initial procedure. The questionnaires used were the EuroQol-5D-3-level, Short Form-36v2, and Gastrointestinal Quality of Life Index. Between treatment groups, no significant differences were found in summarized scores or subscales.

Cost-related outcomes

Two studies compared both procedures in terms of associated costs. Schilling *et al.* (30) compared costs (converted to U.S. dollars) associated with operative time, intensive care and hospital stay, and other resources (e.g. antibiotics, packed red blood cells, and fresh frozen plasma), demonstrating overall expenses to be 74 to 299 percent higher for HP with subsequent restoration of intestinal continuity as compared to PA. Oberkofler *et al.* (23) reported on in-hospital costs in U.S. dollars, but found no significant differences for the index and reversal procedure or both procedures combined. Mean (s.d.) costs associated with the combined procedures were 77.943 ± 50.352 and 75.208 ± 58.002 ($p=0.880$) for HP and PA, respectively. A cost analysis of the DIVA arm of the Ladies trial is to be expected(25).

Discussion

From this systematic review and meta-analysis of the available evidence on PA versus HP for perforated diverticulitis with purulent or fecal peritonitis, several arguments can be identified to support the choice of PA over HP. Firstly, no difference in mortality and morbidity after the index procedure were found between both procedures. Secondly, PA patients were more likely to have their stoma reversed and to be stoma free during follow-up, as compared to HP patients. In addition, the occurrence of reversal-related morbidity was less likely in the PA group.

Although in recent years other meta-analyses on this topic have been published, the present study included the recently published Ladies trial (25), which allowed for the analysis of a larger cohort of patients from randomized studies. Moreover, as compared to these previous review articles, a more extensive scope of outcomes (e.g. patient-reported and cost-related) and results within subgroups of interest (e.g. PA patients with or without ileostomy and Hinchey IV patients) were assessed.

The present results are generally in line with those from previous meta-analyses. With regard to overall mortality from randomized and observational studies, Gachabayov *et al.* (36) and Shaban *et al.* (37) found PA to be favorable over HP, which was also the case in the present quantitative analysis of mortality within the included observational studies. However, in the subgroup analysis of randomized studies in the present study, no difference between treatment groups was demonstrated, which is comparable to the outcomes found by Acuna *et al.* (38). Furthermore, Acuna *et al.* (38) and Gachabayov *et al.* (36) both demonstrated PA patients to be more likely to undergo stoma reversal and be stoma free during follow-up, which is similar to the present results. Recently, two population-based analyses of patients who underwent emergency surgery for acute diverticulitis in the U.S. were published by Lee *et al.* (39) and Gawlick *et al.* (40). Although these studies were not included in this meta-analysis due to the lack of specification on Hinchey grades of included patients, their outcomes provide context to the present findings. The authors show favorable outcomes with regard to mortality after PA as compared to HP and did not find differences in complication rates. Interestingly, a third U.S. population-based study by Cauley *et al.* (41) concluded less favorable on the role of PA. Most importantly, all three studies corrected for potential confounders by means of multivariable regression analyses incorporating factors such as age, BMI, ASA grade, and severity of sepsis. The importance of these potential confounders must be emphasized, as treatment outcomes might be subject to confounding by indication and, thereby, influence the generalizability and interpretation of the present results. Notably, from the quantitative synthesis of baseline characteristics within the included observational studies, this present study indeed found that PA patients were more likely to be younger and have less severe disease in terms of Hinchey grade and MPI scores.

In this review, results were only used for quantitative analyses if they could be assessed specifically for Hinchey III and IV diverticulitis. This strict inclusion and analysis approach was chosen in order to strengthen our conclusion, by avoiding the chance of overestimating true treatment effects through inclusion of patients with less severe

disease entities (e.g. Hinchey II diverticulitis). In addition, another strength of this study is the before mentioned broad scope of outcomes, including cost-related and patient-reported outcomes. Diverticulitis is a costly disease and the incidence of perforated diverticulitis is increasing, therefore, insights into the treatment costs are of interest (15, 42, 43). With benefits such as higher reversal rates and less reversal-related morbidity, PA has the potential to save both direct and indirect medical costs. However, despite its relevance, only two studies reported on the directly associated costs and, therefore, no robust conclusions could yet be drawn (23, 30). Especially, since cost-effectiveness and cost-utility analyses were not described. The presence of a stoma is known to negatively affect factors such as physical function and body image, and consequently, quality of life (44). In this regard, the stoma-related benefits of PA might be able to improve the overall quality of life. Nevertheless, patient-related outcomes could only be identified in the Ladies trial, which showed no differences in outcomes of general and gastrointestinal questionnaires (25). Novel and stronger evidence could be of importance, as the potential beneficial cost-related and patient-reported outcomes could likely be valuable additional arguments to opt for PA. Moreover, it could help with its wider implementation into clinical practice. Particularly, as it is suggested that HP still remains the most widely used procedure in past years (39).

A lack of evidence was identified with regard to the question whether or not it is safe to omit the construction of a defunctioning ileostomy in PA patients, and if so, under what circumstances. Results for PA patients without an ileostomy seemed comparable to those of patients with an ileostomy, albeit that groups were small and at risk for selection bias (25). Similarly, outcomes specifically reported for Hinchey IV patients were scarce and consisted of relatively small groups. It was demonstrated that PA had a significantly better 12-month stoma-free survival as compared to HP within Hinchey IV patients (25). Additionally, some authors found Hinchey IV to be independently associated with an increased morbidity risk, whereas others found no differences between Hinchey III and IV patients (22, 25, 28, 32). Nevertheless, despite the absence of results from larger cohorts of Hinchey IV, the majority of national and international guidelines still state the choice of PA with proximal diversion as a possible treatment option for these patients (5).

There are some limitations to the present study that are important to acknowledge. Most of the included studies consisted of small patient groups and were prone to selection bias due to their retrospective design. More importantly, there was substantial methodological heterogeneity between included studies, both for observational and randomized studies. For instance, differences in intraoperative details, follow-up duration, and definitions of morbidity were present. In order to reduce the effect of this heterogeneity, subgroup analyses of the included RCTs were performed, which for some outcomes showed differences with outcomes from observational studies. Nevertheless, even between these trials several methodological differences existed, such as the moment of randomization, outcome definitions, and follow-up duration.

Interestingly, all four trials were terminated early for reasons of difficulties with patient accrual, which corresponds with the evidence that trials in the acute care setting are

notoriously difficult to conduct and more often lead to early discontinuation (45). However, more importantly, it should clearly be noted that these trial populations might still be a selected patient sample, as the decision to randomize an eligible patient might have been subject to surgeon's preference. A comparison with eligible non-included patients could have helped objectify this potential bias and increase external generalizability, but was only reported in the Ladies trial. Additionally, the trial by Oberkofler and colleagues briefly reported on the numbers of patients that were not screened for eligibility or were not included after screening, but it did not compare patient and disease characteristics of these groups with those of the included patients (23). Furthermore, high-risk patients (e.g. hemodynamically unstable or immunocompromised) were not included or underrepresented in this systematic review. For example, two of the four trials specifically stated hemodynamic instability to be an exclusion criterion. Hence, even though the evidence identifies PA to be the preferred approach to HP, accurate patient selection still remains key. Indeed, in a recent evidence-based EAES/SAGES consensus report it was stated that PA with proximal diversion should be considered over HP in the appropriate clinical setting, but that HP remains the preferred operation for hemodynamically unstable patients (46).

To overcome some of the mentioned methodological problems and to find evidence to fill in the identified gaps in current knowledge, future research might benefit from gathering data in the context of multi-center or (inter)national audit studies. Through multi-center collaboration and prospective (preferably long-term) data collection in a large sample of patients, such a study design has the ability to provide insights into current clinical practice and treatment trends, to analyze outcomes with adjustment for known confounders, as well as to assess outcomes in subgroups such as PA patients with or without ileostomy or Hinchey IV patients. Moreover, the role of emergency laparoscopic sigmoidectomy could potentially be further assessed in this context, as recent promising evidence found it to be superior in terms of postoperative morbidity and hospital stay and concluded it to be feasible in selected patients and performed by experienced hands (34, 47). The DAMASCUS study, a snapshot collaborative audit study on treatment of acute diverticulitis, is an example of such a design and its results are awaited with interest (48). Lastly, with regard to rates of stoma reversal, Hartmann's reversals in particular, it can be hypothesized that restoration of continuity will take place either later or not at all in those patients that have an impaired clinical condition. This is already partly reflected in the reported reasons for non-reversal within the published trials, but is also of great value to assess within the long-term follow-up of existing or novel studies.

In conclusion, this updated systematic review and meta-analysis provides several arguments to prefer PA over HP for the treatment of perforated diverticulitis with purulent or fecal peritonitis. Importantly, between-study heterogeneity needs to be considered whilst interpreting the present results and, above all, the findings should be interpreted within the context of hemodynamically stable and immunocompetent patients. In addition, this study identified gaps in current knowledge that are of interest for future investigation and of which results might further aid accurate surgical decision-making and optimal treatment within the setting of perforated diverticulitis.

Acknowledgements

The authors wish to thank Wichor Bramer and dr. Maarten Engel, biomedical information specialists at the Erasmus University Medical Center (Rotterdam, the Netherlands) for their assistance with the present meta-analysis.

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Tables

Table 1 Study characteristics

Author	Year	Country	Participating centers (n)	Study design	LoE	NOS	MINORS	Study period	Screened patients (n)	Included patients (n)	HP (n)	PA (n)	Hinchey grades (I/II/III/IV)	Follow-up duration	Lost to follow-up (n)	Reporting on stoma reversal
Randomized controlled trials																
Binda	2012	Italy, Turkey, Norway, France, Slovenia, Spain, Poland, Israel	14	RCT	1b	n.a.	n.a.	2001-2010	90	90	56	34	0/0/75/15	Until 30 days after reversal	4 (after reversal)	Yes
Bridoux	2017	France	7	RCT	1b	n.a.	n.a.	June 2008-May 2012	n.r.	102	52	50	0/0/82/20	18 months	0	Yes
Lambrichts	2019	Belgium, Italy, the Netherlands	42	RCT	1b	n.a.	n.a.	July 2010-February 2013; June 2013-June 2016	n.r.	133 (130 mITT)	66	64	0/0/92/38	12 months	1	Yes
Oberkofler	2012	Switzerland	4	RCT	1b	n.a.	n.a.	2006-2009	83 eligible (+52 not assessed for eligibility)	62	30	32	0/0/47/15	Median 47 months (38-55)	0	Yes
Observational studies																
Gooszen	2001	the Netherlands	1	Retro	2b	6	15	1979-1993	277	60	28	32	12/8/32/8	n.r.	n.r.	Yes
Mueller	2011	Germany	1	Retro	2b	6	13	1996-2006	787	73	26	47	26/33/11/3	n.r.	n.r.	No
Regenet	2003	France	1	Pro	2b	7	18	January 1994-November 2001	60	60	33	27	0/0/48/12	12 months	n.r.	Yes (colostomy)
Richter	2006	Germany	1	Retro	2b	6	14	August 2001-August 2003	215	41	5	36	III/IV; numbers not reported	n.r.	n.r.	Yes
Schilling	2001	Switzerland	1	Retro	2b	6	15	January 1994-January 1998	n.r.	55	42	13	0/0/43/12	n.r.	n.r.	Yes
Thaler	2000	Austria	1	Pro	2b	6	13	1988-1998	82	82	62	20	III/IV; numbers not reported	n.r.	n.r.	No

Trenti	2011	Spain	1	Pro	2b	9	18	January 1995-December 2008	234	87	60	27	0/0/72/15	n.r.	n.r.	Yes
Vennix	2016	the Netherlands	28	Retro	2b	9	17	July 2010-July 2014	474	Total: 307, PM: 117	Total: 240, PM: 77	Total: 67, PM: 40	PM: 0/0/96/21	LS (PM): 8 (5-12) months OS (PM): 16 (7-28) months)	n.r.	Yes
Vermeulen	2007	the Netherlands	4	Retro	2b	8	17	January 1995-January 2005	200	200	139	61	35/44/83/38	n.r.	n.r.	No
Wright	2016	the United States	2	Retro	2b	8	17	July 2006-June 2013	n.r.	115	55	53	18/32/51/14	n.r.	n.r.	Yes

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). HP; Hartmann's procedure; LoE, level of evidence; LS, laparoscopic sigmoidectomy; MINORS, Methodological index for non-randomized studies; mITT, modified intention-to-treat analysis; n.a., not applicable; NOS, Newcastle-Ottawa Scale; n.r. = not reported; OS, open sigmoidectomy; PA, primary anastomosis; PM, propensity-matched cohort; Pro, prospective study; Retro, retrospective study; RCT, randomized controlled trial.

Table 2 Patient characteristics

Study	Group	Patients (n)	Sex (M/F (%))	Age (years)	BMI (kg/m ²)	ASA (n (%))	Hinchey III/IV (n (%))	MPI	CRP (mg/l)	WBC (103/μl)	Previous diverticulitis (n (%))	Previous abdominal surgery (n (%))
Randomized controlled trials												
Binda	HP	56	27/29 (48.2/51.8)	65.7 (1.8)	n.r.	n.r.	45/11 (80.4/19.6)	12.7 (0.6)	n.r.	n.r.	n.r.	15 (26.8)
	PA	34	22/12 (64.7/35.3)	63.5 (2.2)	n.r.	n.r.	30/4 (88.2/11.8)	11.4 (0.6)	n.r.	n.r.	n.r.	4 (11.8)
Bridoux	HP	52	23/29 (44.2/55.8)	61.5 (29-92)	26.8 (19.3-44.6)	>ASA I, 43 (82.7)	40/12 (76.5/23.5)	27 (20-43)	n.r.	n.r.	n.r.	n.r.
	PA	50	28/22 (56/44)	61 (25-93)	26.1 (20-43)	>ASA I, 45 (90)	42/8 (84/16)	26 (16-39)	n.r.	n.r.	n.r.	n.r.
Lambrechts	HP	66	41/25 (62/38)	61.7 (11.4)	28 (4.7)	I-II: 37 (63) III-IV: 22 (37)	46/20 (70/30)	23 (17-27)	≤10: 4 (6%), 11-100: 15 (23%), 101-200: 13 (20%), 201-300: 19 (29%), 301-400: 8 (12%), 401-500: 4 (6%), >500 2 (3%), missing: 1 (2%).	14.6 (10.2-20.6)	12 (18%)	Previous laparotomy: 3 (5%)
Oberkofler	PA	64	41/23 (64/36)	62.4 (13.1)	26.3 (4.8)	I-II: 45 (76) III-IV: 14 (24)	46/18 (72/28)	21 (17-26)	≤10: 6 (9%), 11-100: 13 (20%), 101-200: 15 (23%), 201-300: 10 (16%), 301-400: 9 (14%), 401-500: 6 (9%), >500 3 (5%), missing: 2 (3%)	14.2 (9.0-16.9)	12 (19%)	Previous laparotomy: 1 (2%)
	HP	30	9/21 (39/70)	74 (61-81)	24 (22-29)	I-III/IV: 22/8 (73/27)	23/7 (77/23)	22 (16-28)	236 (136-307)	13 (9-17)	n.r.	n.r.
Oberkofler	PA	32	12/20 (38/62)	72 (60-83)	24 (23-28)	I-III/IV: 24/8 (75/25)	24/8 (75/25)	24 (19-28)	194 (67-291)	13 (9-16)	n.r.	n.r.

Study	Group	Patients (n)	Sex (M/F (%))	Age (years)	BMI (kg/m ²)	ASA (n (%))	Hinchey III/IV (n (%))	MPI	CRP (mg/l)	WBC (103/ μ l)	Previous diverticulitis (n (%))	Previous abdominal surgery (n (%))
Observational studies												
Gooszen	HP	28	n.r.	68 (16)	n.r.	n.r.	13/6 (46.4/21.4)	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	32	n.r.	63 (17)	n.r.	n.r.	19/2 (59.4/6.3)	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	26	10/16 (38/62)	67 (13)	n.r.	I (8%), II (16%), III (42%), IV (34%)	9/3 (35/11)	n.r.	n.r.	n.r.	n.r.	n.r.
Regenet	PA	47	26/21 (53/47)	63 (12)	n.r.	I (36%), II (33%), III (25%), IV (6%)	2/0 (4/0)	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	33	18/15 (54.5/45.5)	67.3 (12.9)	n.r.	I (3%), II (51.5%), III (39.4%), IV (6.1%)	24/9 (72.7/27.3)	24.5 (6.7)	182 (130)	13.5 (7.3)	n.r.	n.r.
	PA	27	10/17 (37/63)	64.8 (16.5)	n.r.	I (3.7%), II (48.2%), III (44.4%), IV (3.7%)	24/3 (88.9/11.1)	21.2 (5.8)	133 (131)	15.3 (6.5)	n.r.	n.r.
Richter	Overall	41	19/22 (46.3/53.7)	60 (2)	n.r.	2.7 (0.2)	n.r.	20.5 (1.5)	127 (22)	n.r.	n.r.	n.r.
Schilling	HP	5	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	36	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	42	20/22 (47.6/52.4)	68 (10)	n.r.	2.5 (2-3)	33/9 (78.6/21.4)	23 (8)	159 (68)	n.r.	n.r.	n.r.
	PA	13	6/7 (46.2/53.8)	65 (12)	n.r.	2.5 (2-3)	10/3 (76.9/23.1)	21 (7)	139 (77)	n.r.	n.r.	n.r.
Thaler	HP	62	25/37 (40.3/59.7)	72 (15)	n.r.	IV/V: 44 (71)	n.r.	23 (8)	n.r.	n.r.	n.r.	n.r.
	PA	20	6/14 (30/70)	70 (13)	n.r.	IV/V: 7 (35)	n.r.	18 (7)	n.r.	n.r.	n.r.	n.r.
Trenti	HP	60	34/26 (56.7/43.3)	69.7 (12.7)	n.r.	I (6.7%), II (13.3%), III (33.3%), IV (46.7%)	46/14 (76.7/23.3)	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	27	19/8 (70.4/29.6)	58.1 (16.3)	n.r.	I (29.6%), II (51.9%), III (18.5%), IV (0%)	26/1 (96.3/3.7)	n.r.	n.r.	n.r.	n.r.	n.r.

Study	Group	Patients (n)	Sex (M/F (%))	Age (years)	BMI (kg/m ²)	ASA (n (%))	Hinchey III/IV (n (%))	MPI	CRP (mg/l)	WBC (10 ³ /μl)	Previous diverticulitis (n (%))	Previous abdominal surgery (n (%))
Vennix	Overall (open)	263	138/125 (52.5/47.5)	62.6 (13.9)	27.0 (5.8)	I (16.5%), II (45.6%), III (32.3%), IV (5.7%)	173/90 (65.3/34.7)	21.1 (5.6)	221 (142)	14.7 (11.4)	50 (19.1)	26 (9.9)
	Overall (laparoscopic)	44	30/14 (68.2/31.8)	56.2 (13.5)	25.6 (3.9)	I (24.2%), II (39.4%), III (33.3%), IV (3%)	34/10 (76.7/23.3)	19.1 (5.4)	156 (114)	15.2 (8.7)	7 (16.7)	1 (2.3)
	HP	240	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	67	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Vermeulen	HP	139	64/75 (46/54)	69 (13)	n.r.	I (18%), II (22%), III (33%), IV (27%)	62/33 (45/24)	21 (8)	n.r.	n.r.	n.r.	n.r.
	PA	61	25/36 (41/59)	62 (15)	n.r.	I (28%), II (31%), III (30%), IV (11%)	21/5 (34/8)	17 (6)	n.r.	n.r.	n.r.	n.r.
Wright	Overall (colorectal)	62	25/37 (40.3/59.7)	62.7 (13.3)	28.4 (16-51.3)	I (3.2%), II (41.9%), III (45.2%), IV (9.7%)	20/7 (32.3/11.3)	n.r.	n.r.	n.r.	36 (58.1)	n.r.
	Overall (general)	53	27/26 (50.9/49.1)	63.4 (14.4)	26.8 (18.9-54.1)	I (3.8%), II (47.2%), III (32.1%), IV (17.0%)	31/7 (58.5/13.2)	n.r.	n.r.	n.r.	13 (24.5)	n.r.
	HP	55	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	53	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). ASA: American Society of Anesthesiologists; BMI, body mass index; CRP, C-reactive protein; HP, Hartmann's procedure; MPI, Mannheim Peritonitis Index; n.r., not reported; PA, primary anastomosis; WBC, white blood cell count.

Table 3 Outcomes of the index operation (1/2)

Study	Group	Patients (n)	Mortality	Mortality period	Morbidity	Morbidity period	Clavien-Dindo	Clavien-Dindo period	Reinterventions	LOS (days)	ICU stay
Randomized controlled trials											
Binda	HP	56	6 (10.7%)	30-day	26 (46.4%)a	30-day	n.r.	n.a.	1 (1.8%)	n.r.	n.r.
	PA	34	1 (2.9%)	30-day	12 (35.3%)a	30-day	n.r.	n.a.	1 (2.9%)	n.r.	n.r.
Bridoux	HP	52	1 (3.8%)	Postoperative period	22 (42.3%)a	n.s.	7 (13.5%)b	n.s.	2 (3.8%) abscess	11 (4-88)	9.5 (3-27)
	PA	50	1 (2%)	Postoperative period	27 (54%)a	n.s.	7 (14%)b	n.s.	1 (2%) abscess, 2 (4%) anastomotic leakage	11.5 (3-53)	9.5 (1-71)
Lambrecht	HP	66	2 (3%)	In-hospital/30 days	Major: 8 (12%)c Minor: 26 (39%)c Overall: 29 (44%)c	In-hospital/30 days	12 (18%)d	90-day	4 (6%) surgical	9.0 (7-15)	2.0 (1-11)
	PA	64	4 (6%)	In-hospital/30 days	Major: 9 (14%)c Minor: 19 (30%)c Overall: 25 (39%)c	In-hospital/30 days	9 (14%)d	90-day	4 (6%) surgical	9.5 (7-13)	1.5 (1-3)
Oberkofler	HP	30	4 (13%)	In-hospital	Overall: 24 (80%)	n.s.	12 (40%)d	n.s.	n.r.	18 (14-27)	2 (1-3)
	PA	32	3 (9%)	In-hospital	Overall: 27 (84%)	n.s.	14 (44%)d	n.s.	n.r.	16 (13-25)	1 (1-4)
Observational studies											
Gooszen	HP	Overall: 28 Hinchey III/ IV: 19	4/19 (21.1%)	In-hospital	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
	PA	Overall: 32 Hinchey III/ IV: 21	3/21 (11.1%)	In-hospital	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
Mueller	HP	26	Hinchey III: 2 Hinchey IV: 2	In-hospital	Major: Hinchey III: 3 Hinchey IV: 3	In-hospital	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
	PA	47	Hinchey III: 1	In-hospital	Major: Hinchey III: 3	In-hospital	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
Regenet	HP	33	4 (12.1%)	In-hospital/30 days	n.r.	n.r.	n.r.	n.r.	4 (12.1%)	n.r.	9.8 (20.8)
	PA	27	3 (11.1%)	In-hospital/30 days	n.r.	n.r.	n.r.	n.r.	2 (7.4%)	n.r.	5.3 (12.4)
Richter	Overall	41	7 (17.1%)	n.s.	n.r.	n.r.	n.r.	n.r.	-	n.r.	5 (1.4)
	HP	5	3 (60%)	n.s.	n.r.	n.r.	n.r.	n.r.	0	n.r.	-
	PA	36	4 (11.1%)	n.s.	n.r.	n.r.	n.r.	n.r.	1 (2.8%)	n.r.	-

Study	Group	Patients (n)	Mortality	Mortality period	Morbidity	Morbidity period	Clavien-Dindo	Clavien-Dindo period	Reinterventions	LOS (days)	ICU stay
Schilling	HP	42	4 (9.5%)	n.s.	5 (11.9%) major, 9 (21.4%) minor	n.s.	n.r.	n.r.	n.r.	15.4 (6.6) regular ward	2.1 (5.1)
	PA	13	1 (7.7%)	n.s.	1 (7.7%) major, 5 (38.5%) minor	n.s.	n.r.	n.r.	n.r.	17.4 (10.9) regular ward	0.8 (1.4)
Thaler	HP	62	22 (35%)	n.s.	7 (11%) surgical, 13 (21%) overall	n.s.	n.r.	n.r.	n.r.	22 (20)	21 (37%)
	PA	20	4 (20%)	n.s.	6 (30%) surgical, 7 (35%) overall	n.s.	n.r.	n.r.	n.r.	23 (12)	5 (28%)
Trenti	HP	60	27 (45%)	n.s.	52 (86.7%) ^a	n.s.	n.r.	n.r.	12 (20%)	27.9 (22.8)	n.r.
	PA	27	2 (7.4%)	n.s.	13 (48.1) ^a	n.s.	n.r.	n.r.	3 (11.1%)	15.1 (9.4)	n.r.

Continuous data are median (interquartile range), or mean (standard deviation), or mean (range). a = overall morbidity; b = Clavien-Dindo III-V; c = major morbidity defined as surgical reintervention, percutaneous abscess drainage, fascial dehiscence, urosepsis, myocardial infarction, renal failure, and respiratory insufficiency; minor morbidity defined as surgical site infection, postoperative ileus, pneumonia, delirium, urinary tract infection, abscess without drainage, thrombosis, cardiac complications, and overall morbidity defined as major and minor complications combined; d = Clavien-Dindo IIIb-V; e = major defined as anastomotic leakage, leakage of the Hartmann's stomp, or stoma necrosis; f = Clavien-Dindo I-V; g = major complications defined as those which required change in therapy or prolonged therapy, minor not defined. HP, Hartmann's procedure; ICU, intensive care unit; LOS, length of stay; n.r., not reported; n.s., not reported separately; n.s., not specified; PA, primary anastomosis; PM, propensity-matched cohort.

Table 4 Outcomes of the index operation (2/2)

Study	Group	(Ongoing) sepsis	Anastomotic leakage	Intra-abdominal abscess	Abscess drainage	SSI	Other infectious complications	Organ dysfunction	Fascial dehiscence	Incisional hernia	Parastomal hernia	Malignancy
Randomized controlled trials												
Binda	HP	n.r.	1 (1.8%) (rectal stump leak)	6 (10.7%)	6 (10.7%)	11 (19.6%) superficial, 9 (16.1%) deep	4 (7.1%) pneumonia, 3 (5.4%) UTI	6 (10.7%)	n.r.	n.r.	n.r.	1 (1.8%)
	PA	n.r.	1 (2.9%)	0	0	9 (26.5%) superficial, 6 (17.6%) deep	2 (5.9%) pneumonia	1 (2.9%)	n.r.	n.r.	n.r.	2 (5.9%)
Bridoux	HP	0	0	4 (7.7%)	2 (3.8%)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	2 (3.8%)
	PA	1 (2%)	2 (4%)	2 (4%)	1 (2%)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	3 (6%)
Lambrechts	HP	2 (3%)	0	7 (10.6%)	2 (3%)	8 (12%)	5 (8%) pneumonia, 2 (3%) UTI	4 (6%) respiratory failure, 3 (5%) renal failure	0	5 (8%)	10 (16%)	0
	PA	4 (6%)	0	2 (3%)	2 (3%)	7 (11%)	2 (3%) UTI	1 (2%) respiratory failure, 1 (2%) renal failure	3 (5%)	3 (5%)	0	2 (3%)
Oberkofler	HP	2 (6.7%)	0	6 (20%)*	n.r.	13 (43.3%)	3 (10%) UTI	6 (20%) respiratory; 5 (16.7%) cardiovascular; 5 (16.7%) renal failure	3 (10%)	n.r.	n.r.	n.r.
	PA	4 (12.5%)	1 (3.1%)	2 (6.3%)*	n.r.	11 (34.4%)	1 (3.1%)	7 (21.9%) respiratory; 3 (9.4%) cardiovascular; 2 (6.3%) renal failure	4 (12.5%)	n.r.	n.r.	n.r.
Observational studies												
Gooszen	HP	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
	PA	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
Mueller	Overall	n.r.s.	Hinchey III: 3	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
	HP	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
Regenet	PA	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.	n.r.s.
	HP	2 (6.1%)	2 (6.1%)	3 (9.1%)†	n.r.	9 (27.3%)	n.r.	7 (21.2%) respiratory complication; 1 (3%) cardiac complication; 2 (6.1%) renal insufficiency	1 (3%)§	n.r.	n.r.	n.r.

Study	Group	(Ongoing) sepsis	Anastomotic leakage	Intra-abdominal abscess	Abscess drainage	SSI	Other infectious complications	Organ dysfunction	Fascial dehiscence	Incisional hernia	Parastomal hernia	Malignancy
	PA	2 (7.4%)	3 (11.1%)	1 (3.7%) [†]	n.r.	2 (7.4%)	n.r.	4 (14.8%) respiratory complication; 0 cardiac complication; 0 renal insufficiency	2 (7.4%) [§]	n.r.	n.r.	n.r.
Richter	HP	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	n.r.	1 (2.8%)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Schilling	HP	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Thaler	HP	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	n.r.	3 (15%) fascial of anastomotic dehiscence	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Trenti	HP	14 (23.3%)	0	8 (13.3%)	5 (8.3%)	19 (31.7%)	17 (28.3%) pulmonary infection/insufficiency	9 (11.4%) cardiac decompensation	7 (11.7%) [§]	n.r.	n.r.	n.r.
	PA	1 (3.7%)	3 (11.1%)	0	0	10 (37%)	1 (3.7%) pulmonary infection/insufficiency	1 (3.7%) cardiac decompensation	0	n.r.	n.r.	n.r.

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). [†]Defined as intra-abdominal infection. [‡]Defined as secondary peritonitis or intra-abdominal abscess. [§]Defined as wound dehiscence. HP, Hartmann's procedure; n.a., not applicable; n.r., not reported; n.r.s., not reported separately; PA, primary anastomosis; SSI, surgical site infection; UTI, urinary tract infection.

Figures

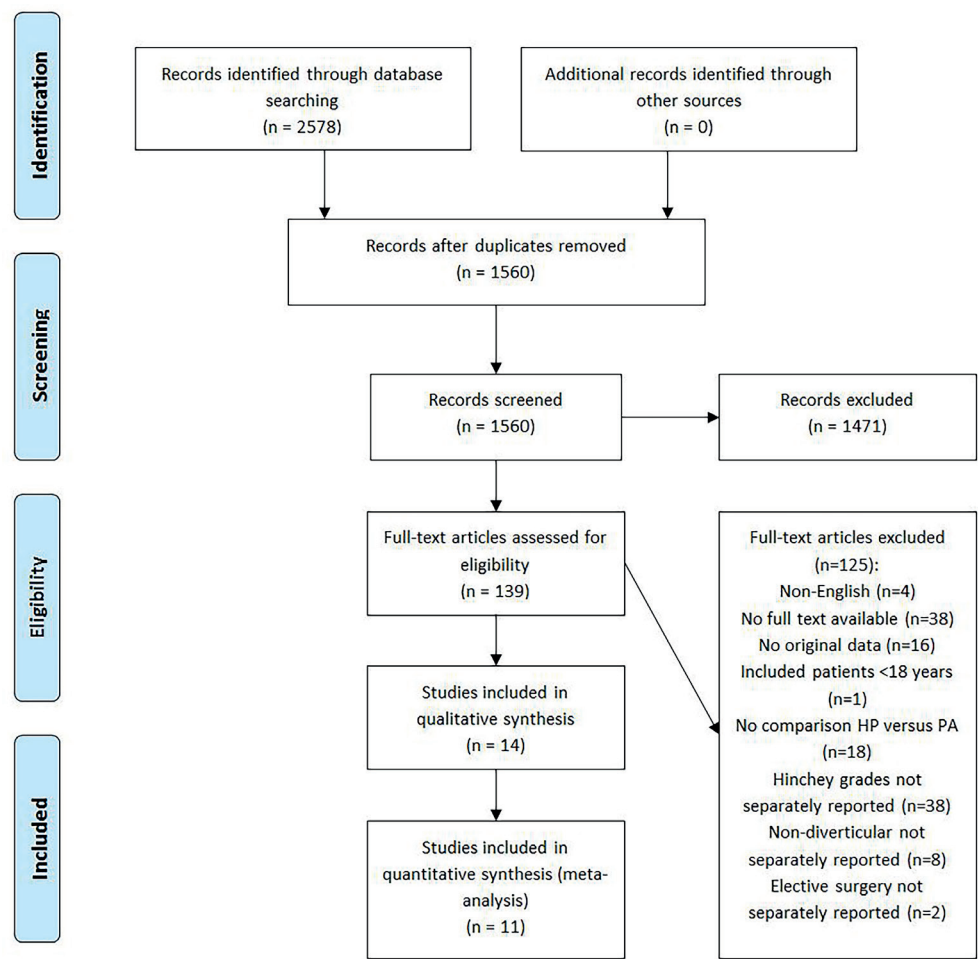


Figure 1 PRISMA flow diagram

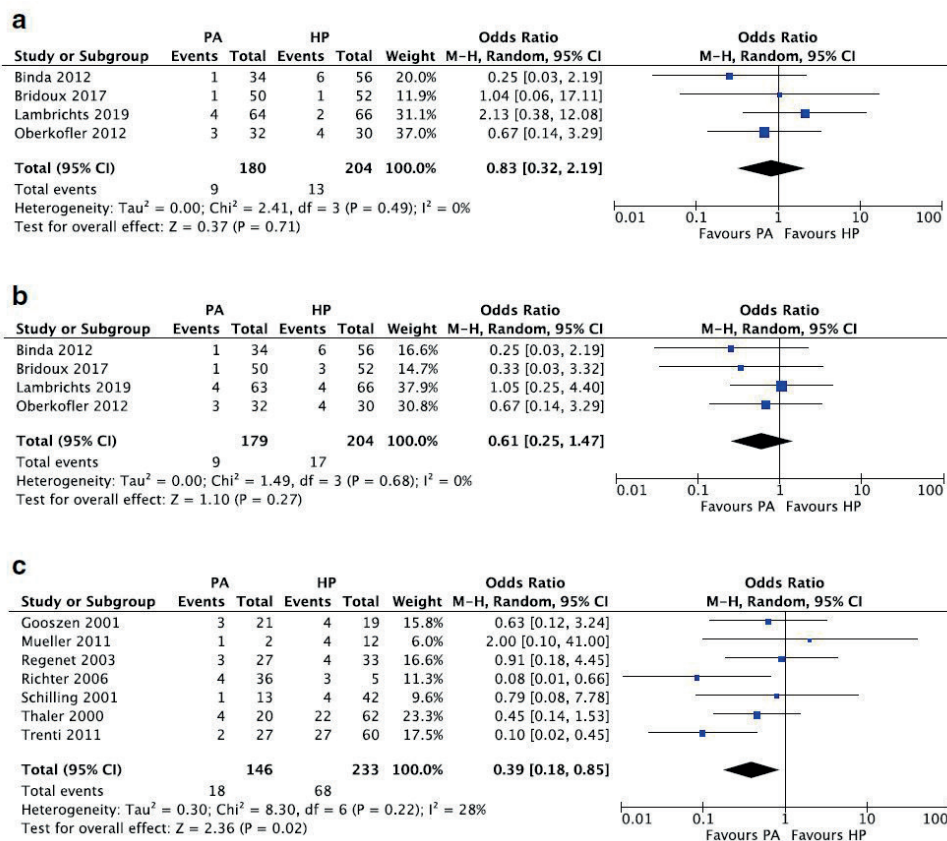


Figure 2 Quantitative analyses of a. short-term mortality rates in randomized controlled trials, b. long-term mortality rates in randomized controlled trials, and c. overall mortality rates during follow-up in observational studies.

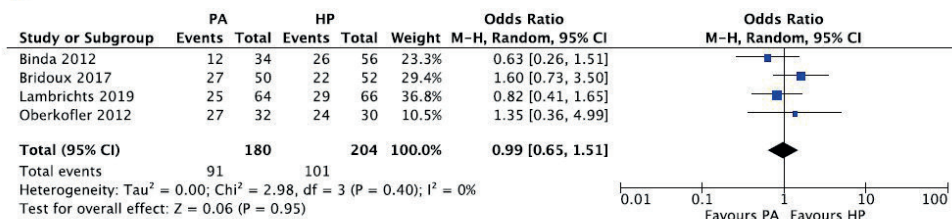
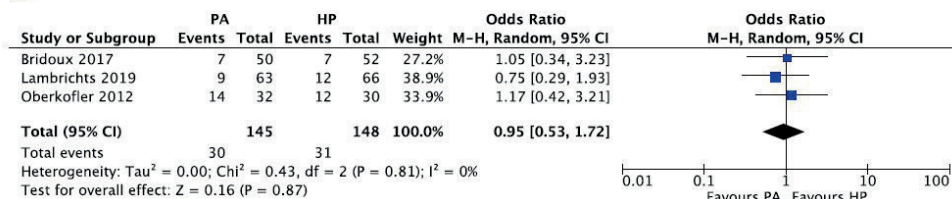
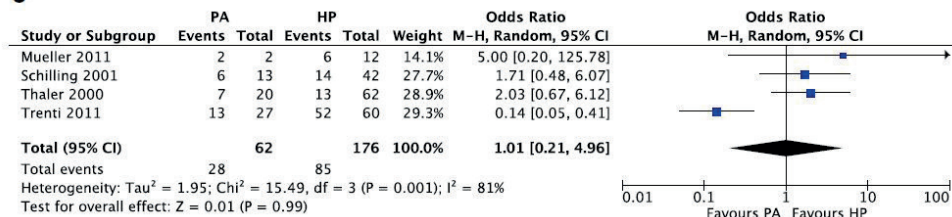
a**b****c**

Figure 3 Quantitative analyses of a. overall morbidity rates in randomized controlled trials, b. short-term serious complications in randomized controlled trials, and c. overall morbidity rates in observational studies.

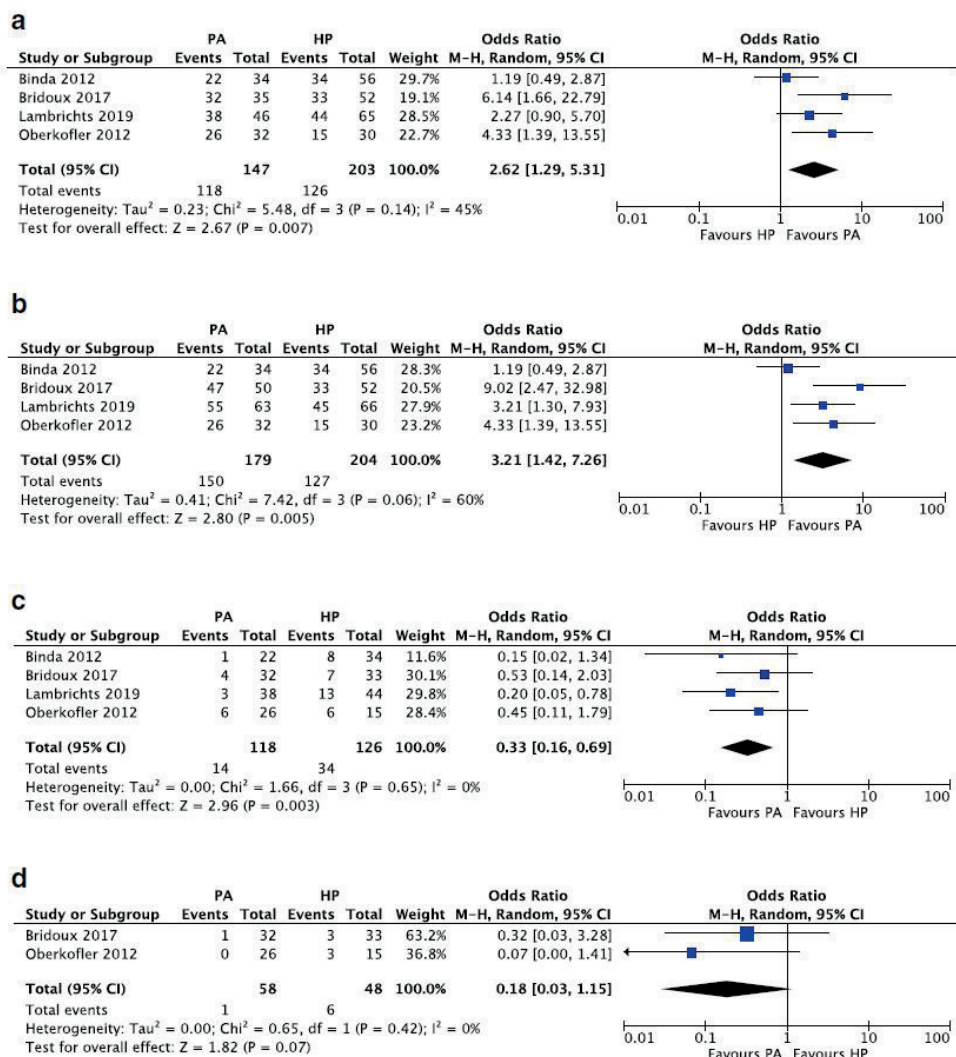


Figure 4 Quantitative analyses of randomized controlled trials: a. reversal rates of constructed stomas, b. number of stoma-free patients, c. reversal-related morbidity, d. reversal-related serious complications.

Appendix

Search syntaxes and results per database

embase.com	1211	1199
Medline Ovid	764	179
Web of science	569	176
Cochrane CENTRAL	34	6
Total	2578	1560

embase.com

('hartmann procedure'/de OR 'hartmann operation'/de OR (hartman* OR ((non-restor* OR nonrestor*) NEAR/3 resect*)):ab,ti OR (((('diverticulitis'/exp OR diverticulosis/exp) AND ('perforation'/exp OR 'acute disease'/de OR peritonitis/de)) OR ((diverticul* AND (perforat* OR complicat* OR acute OR peritonitis)) OR Hinchey*)):ab,ti) AND ('colostomy'/exp OR 'colon stoma'/de OR (colostom* OR (colon* NEAR/3 stoma*) OR (staged NEAR/3 procedure*) OR two-stage* OR 2-stage*)):ab,ti))) AND ('anastomosis'/de OR 'ileostomy'/de OR (((primar* OR end-to-end OR end-to-side OR side-to-end OR side-to-side) NEAR/3 anastomos*) OR ileostom*)):ab,ti)

Medline Ovid

((hartman* OR ((non-restor* OR nonrestor*) ADJ3 resect*)):ab,ti. OR (((exp Diverticulitis/ OR Diverticulum/ OR Diverticulosis, Colonic/) AND (exp Intestinal Perforation/ OR Acute Disease/ OR Peritonitis/)) OR ((diverticul* AND (perforat* OR complicat* OR acute OR peritonitis)) OR Hinchey*)):ab,ti.) AND (colostomy/ OR (colostom* OR (colon* ADJ3 stoma*) OR (staged ADJ3 procedure*) OR two-stage* OR 2-stage*)):ab,ti.))) AND (Anastomosis, Surgical/ OR Ileostomy/ OR (((primar* OR end-to-end OR end-to-side OR side-to-end OR side-to-side) ADJ3 anastomos*) OR ileostom*)):ab,ti.)

Web of science

TS=(((hartman* OR ((“non-restor*” OR nonrestor*) NEAR/2 resect*)) OR (((diverticul* AND (perforat* OR complicat* OR acute OR peritonitis)) OR Hinchey*)) AND ((colostom* OR (colon* NEAR/2 stoma*) OR (staged NEAR/2 procedure*) OR two-stage* OR “2-stage*”)))) AND (((primar*) NEAR/2 anastomos*) OR ileostom*))

Cochrane CENTRAL

((hartman* OR ((non next restor* OR nonrestor*) NEAR/3 resect*)):ab,ti OR (((diverticul* AND (perforat* OR complicat* OR acute OR peritonitis)) OR Hinchey*)):ab,ti) AND ((colostom* OR (colon* NEAR/3 stoma*) OR (staged NEAR/3 procedure*) OR two next stage* OR 2 next stage*)):ab,ti))) AND (((primar*) NEAR/3 anastomos*) OR ileostom*)):ab,ti)

Supplemental Tables

Supplemental Table 1 Operative characteristics of the index procedure

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Night surgery (n)	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Stoma construction (n)	Drain placement	Intraoperative lavage
Randomized controlled trials													
Binda	Overall	90	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	Closed suction drainage along left paracolic gutter	Lavage of the peritoneal cavity with normal saline (0.9% NaCl)
Bridoux	HP	56	154.4 (6.6)	n.r.	36 (63.6)	n.r.	53/3 (94.6/5.4)	0	n.r.	n.a.	56 (100)	52 (93)	6.1 (0.6) liter
	PA	34	167.3 (8.5)	n.r.	15 (44.1)	n.r.	30/4 (88.2/11.8)	0	n.r.	Double-stapled anastomosis	34 (100)	32 (94)	4.5 (0.5) liter
Lambrichts	HP	52	120 (40-360)	23 (45.1%)*	22 (43.1)	n.r.	n.r.	n.a.	n.r.	n.r.	52	Discretion of surgeon	Discretion of surgeon
	PA	50	175.5 (74-320)	24 (48%)*	19 (38)	n.r.	n.r.	n.a.	End-to-end or side-to-end	n.r.	35	Discretion of surgeon	Discretion of surgeon
Overall		130	n.r.	-	n.r.	-	-	0	-	-	-	Decision left at the surgeon's discretion	n.r.
HP		66	118 (95.5-135.3)	57 (86%)*	n.r.	≤100: 30 (45%), 101-500: 24 (36%), 501-1000: 3 (5%), missing: 9 (14%)	46/20 (70/30)	0	1 (2%) STS	1 (2%) manual	65 (98%)	21 (32%)	n.r.

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Night surgery (n)	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Stoma construction (n)	Drain placement	Intraoperative lavage
Oberkofler	PA	64	125 (110-154)	58 (91%)#	n.r.	≤100: 31 (48%), 101-500: 20 (31%), 501-1000: 4 (6%), >1000: 1 (2%), missing: 8 (13%)	47/17 (73/27)	0	18 (28%) ETE, 3 (5%) ETS, 9 (14%) STS, 20 (31%) STE, missing 6 (9%)	11 (17%) manual, 43 (67%) stapler, 2 (3%) missing	17 (27%)	27 (44%)	n.r.
	Overall	62	180 (147-225)	61/1 (98/2%)†	n.r.	100 (200-575)	n.r.	n.a.	n.r.	n.r.	-	n.r.	Decided by individual surgeons
	HP	30	168 (130-220)	31/1 (97/3%)†	n.r.	300 (100-600)	n.r.	n.a.	n.r.	n.r.	30 EC	n.r.	n.r.
Observational studies	PA	32	208 (150-223)	30/0 (100/0%)†	n.r.	200 (100-500)	n.r.	n.a.	n.r.	Transanal circular stapling	29 LI; 3 EC	n.r.	Colonic cleaning in 50%
	HP	28	150 (60-240)	28 (100%)\$	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	28 (100)	n.r.	n.r.
	PA	32	172 (75-300)	32 (100%)\$	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	7 LI (21.9); 25 LTC (78.1)	n.r.	n.r.
Mueller	HP	26	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	Hinchev III: 9 EC Hinchev IV: 3 EC	n.r.	n.r.
	PA	47	n.r.	n.r.	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	Hinchev III: 2 LI Hinchev IV: n.r.	n.r.	n.r.
	Overall	60	n.r.	Five surgeons with the same level of training participated	n.r.	n.r.	60/0 (100/0)	n.a.	n.a.	n.r.	-	Pouch of Douglas was always drained	Peritoneal lavage in all, with warm saline (mean 10 l (range 7-120))

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Night surgery (n)	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Stoma construction (n)	Drain placement	Intraoperative lavage
Richter	HP	33	172 (22)	-	n.r.	n.r.	33/0 (100/0)	n.a.	n.a.	n.r.	33 EC	-	Irrigation of colon and rectal stump with saline (37°C)
	PA	27	225 (39)	-	n.r.	n.r.	27/0 (100/0)	n.a.	STE in all patients	n.r.	27 LI	-	-
	Overall	41	131.4 (5)	Staff surgeons (8), certified surgeons (5), residents under staff supervision (3)	n.r.	221 (35)	n.r.	n.a.	n.r.	n.r.	-	n.r.	Abdominal lavage with 30 liter of warm Ringer's lactate solution
Schilling	HP	5	n.r.	-	n.r.	-	n.r.	n.a.	n.r.	n.r.	5 EC	n.r.	-
	PA	36	n.r.	-	n.r.	-	n.r.	n.a.	n.r.	n.r.	4 LI	n.r.	-
	HP	42	198 (60)	n.r.	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	42 EC	n.r.	Extensive abdominal lavage with at least 20 liter warm (37°C) Ringer's lactate
Thaler	PA	13	198 (72)	n.r.	n.r.	n.r.	n.r.	n.a.	n.r.	Two-layer technique with absorbable suture	13 LI	n.r.	Extensive abdominal lavage with at least 20 liter warm (37°C) Ringer's lactate
	HP	62	n.r.	All procedures performed by eight experienced staff surgeons	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	62 EC	n.r.	n.r.

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Night surgery (n)	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Stoma construction (n)	Drain placement	Intraoperative lavage
Trenti	PA	20	n.r.	All procedures performed by eight experienced staff surgeons	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	0	n.r.	n.r.
	HP	60	n.r.	6 CS (27.3%), 23 (67.6%)●	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	60 EC	n.r.	Extensive intraabdominal lavage with warm saline solution
	PA	27	n.r.	16 CS (72.7%), 11 (32.4%)●	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	5 LI	n.r.	Extensive intraabdominal lavage with warm saline solution
Vennix	PM (open)	78	96.5 (87-120)	76 (97.4%)†	n.r.	15 (42)	78	n.r.	n.r.	n.r.	12/27 (44.4%)	n.r.	n.r.
	PM (laparoscopic)	39	127 (105-159)	38 (97.4%)†	n.r.	14 (74)	39	Overall (laparoscopic): 51/153 (33.3%)	n.r.	n.r.	8/13 (61.5%)	n.r.	n.r.
Vermeulen	HP	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	139	n.r.	89 GS (64%), 50 CS (36%)	DOH (64%), 50 OOH (36%)	n.r.	n.r.	n.a.	n.r.	n.r.	139 EC	n.r.	n.r.
	PA	61	n.r.	38 GS (62%), 23 CS (38%)	DOH (45%), 34 OOH (55%)	n.r.	n.r.	n.a.	n.r.	n.r.	16 (26%) LI	n.r.	n.r.

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Night surgery (n)	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Stoma construction (n)	Drain placement	Intraoperative lavage
Wright	Overall (colorectal)	62	154 (30-482)	22 PGY3-4 (35.5%), 40 PGY5-6 (64.5%)	n.r.	n.r.	10 (16.1)	2 (20)	n.r.	n.r.	-	n.r.	n.r.
	Overall (general)	53	127 (39-239)	26 PGY3-4 (49.1%), 27 PGY5-6 (50.9%)	n.r.	n.r.	5 (9.4)	2 (40)	n.r.	n.r.	-	n.r.	n.r.
	HP (colorectal)	21	137	n.a.	n.r.	n.r.	-	-	n.r.	n.r.	21 EC	n.r.	n.r.
	HP (general)	34	128	n.a.	n.r.	n.r.	-	-	n.r.	n.r.	34 EC	n.r.	n.r.
	PA (colorectal)	38	n.r.	n.a.	n.r.	n.r.	-	-	n.r.	n.r.	28 LI	n.r.	n.r.
	PA (general)	15	n.r.	n.a.	n.r.	n.r.	-	-	n.r.	n.r.	0 LI	n.r.	n.r.

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). *Resident as first surgeon. §In all cases, the operation was performed by two surgeons of whom at least one had colorectal expertise. #Gastrointestinal surgeon present. †Presence of board-certified surgeon. •Calculated including only patients with a peritonitis severity score <11. CS, colorectal surgeon; DOH, during office hours; EC, end colostomy; ETE, end-to-end anastomosis; ETS, end-to-side anastomosis; GS, general surgeon; HP, Hartmann's procedure; LI, loop ileostomy; LTC, loop transverse colostomy; n.a., not applicable; n.r., not reported; OOH, outside office hours; PA, primary anastomosis; PGY, postgraduate year. PM, propensity-matched cohort; STE, side-to-end anastomosis; STS, side-to-side anastomosis.

Supplemental Table 2 Operative characteristics of the reversal procedure

Study	Group	Patients (n)	Operating time (min)	Surgical expertise	Blood loss (ml)	Open/laparoscopic	Conversion	Anastomotic configuration	Anastomotic construction	Drain placement	Intraoperative lavage
Randomized controlled trials											
Binda	HP	34	n.r.	n.r.	n.r.	Open	n.a.	n.r.	Linear stapler	n.r.	n.r.
	PA	22	n.r.	n.r.	n.r.	Performed with trephine incision	n.a.	Functional ETE	Cutting stapler	n.r.	n.r.
Bridoux	Overall	65	120 (30-510)	29 (44.6%)*	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
	HP	33	170 (80-510)	13 (39.4%)*	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
Lambrechts	PA	32	70 (30-300)	16 (50%)*	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
	HP	44	n.r.	n.r.	n.r.	24/20	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	38	n.r.	n.r.	n.r.	Ileostomy reversal: 34, colostomy reversal: 3/1	n.r.	n.r.	n.r.	n.r.	n.r.
Oberkofler	Overall	41	110 (66-158)	n.r.	25 (5-50)	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
	HP	15	183 (150-225)	n.r.	45 (5-150)	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
PA		26	73 (60-90)	n.r.	20 (5-40)	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
Observational studies											
Gooszen	HP	13	172 (90-195)	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
	PA	24	75 (30-150)	n.r.	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
Wright (colorectal)	Overall	38	78 (33-406)	n.a.	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.
	Overall (general)	22	167 (85-473)	n.a.	n.r.	n.r.	n.a.	n.r.	n.r.	n.r.	n.r.

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). *Resident as first surgeon. CS, colorectal surgeon; ETE, end-to-end anastomosis; HP, Hartmann's procedure; n.a., not applicable; n.r., not reported; NCS, non-colorectal surgeon; PA, primary anastomosis; STE, side-to-end anastomosis; STS, side-to-side anastomosis.

Supplemental Table 3 Summarized outcomes of quantitative analyses of the baseline characteristics in observational studies

Characteristic	Pooled outcome*	95% CI	P value	I ² (%)	Chi ²	P value	Studies (n)
Sex (% female)	2.14	0.79, 5.75	0.13	54	6.47	0.09	4
Mean age (years)	-4.84	-9.41, -0.27	0.04	39	4.93	0.18	4
ASA I-II (%)	3.92	0.21, 72.52	0.36	93	14.29	0.0002	2
Hinchey III (%)	2.45	1.30, 4.63	0.006	0	3.53	0.62	6
Mean MPI	-3.58	-5.70, -1.47	0.0009	0	1.08	0.58	3
Mean CRP	-29.58	-67.74, 8.58	0.13	0	0.49	0.48	2

*Pooled outcomes were OR for dichotomous variables and MD for continuous variables. Quantitative analysis was not possible for BMI, previous diverticulitis, previous abdominal surgery, and white blood cell count, as data was insufficient for these characteristics.

Supplemental Table 4 Details of randomized controlled trials

Study	Inclusion criteria	Exclusion criteria	Total sample size (n)	Patients screened for eligibility (n)	Patients included in (modified) intention-to-treat analyses (n)				Cross-overs	Moment of randomization	Primary endpoint	Trial accrual
					HP	PA	HP	PA				
Binda	- ≥ 18 years of age - perforated left colonic diverticulitis with peritonitis	- failure to sign consent - peritonitis secondary to perforated diverticulitis of right colon	600	n.r.	56	34	None	None	None	Preoperative	n.r.	Early termination, because of slow patient accrual.
Bridoux	- ≥ 18 years of age - perforated diverticulitis with purulent or fecal peritonitis	- physical states that prevented patient's participation (e.g. septic shock or multivisceral failure) - failure to provide consent	246	n.r.	- Primary analysis: 52 - Stoma reversal analysis: 33	- Primary analysis: 50 - Stoma reversal analysis: 32	- 1 total coloproctectomy	- 5 cross-overs to HP	Preoperative	Rate of mortality after index and reversal operation.	Early termination, because of recruitment difficulties.	
Lambrichts	- patients 18-85 years of age - clinical suspicion of perforated diverticulitis with peritonitis and free air/fluid on abdominal radiography or CT - signed informed consent	- dementia - previous sigmoidectomy - previous pelvic radiotherapy - chronic steroid treatment (≥ 20 mg daily) - preoperative shock requiring inotropic support	236	n.r.	- Primary analysis: 66 - Stoma reversal analysis: 44	- Primary analysis: 64 - Stoma reversal analysis: 38	- 1 cross-over to PA	- 7 cross-overs to HP - 1 cross-over to LL	Intraoperative	12-month stoma-free survival.	Early termination, because of slow patient accrual.	

Study	Inclusion criteria	Exclusion criteria	Total sample size (n)	Patients screened for eligibility (n)	Patients included in (modified) intention-to-treat analyses (n)			Cross-overs		Moment of randomization	Primary endpoint	Trial accrual
					HP	PA	PA	HP	PA			
Oberkofler	- ≥ 18 years of age - perforated left colonic diverticulitis with peritonitis - informed consent	- patients without generalized peritonitis (Hinchey I and II) - evidence of metastasis at presentation	136	83 (14 did not meet inclusion criteria, 7 declined to participate)	- Primary analysis: 30 - Stoma reversal analysis: 15	- Primary analysis: 32 - Stoma reversal analysis: 26		- 1 cross-over to PA	- 3 cross-overs to HP	Preoperative	Overall postoperative complication rate (percent yes/no) including the first (colon resection) and an interim analysis showing operation, assessed according to the Clavien-Dindo classification.	Early termination, because of decreasing accrual rates and an interim analysis showing significant differences of relevant secondary endpoints.

HP, Hartmann's procedure; LL, laparoscopic lavage; n.r., not reported; PA, primary anastomosis.

Supplemental Table 5 Numbers needed to treat

Outcomes	Risk difference (95% CI)	Risk Ratio (95% CI)	Assumed control risk	Numbers needed to treat*
Reversal rate constructed stomas	0.20 (0.08, 0.31)	1.30 (1.12, 1.52)	0.62 (126/203)	5
Number of stoma-free patients	0.22 (0.10, 0.33)	1.34 (1.16, 1.55)	0.62 (127/204)	5
Overall morbidity after reversal procedure	-0.17 (-0.26, -0.08)	0.44 (0.18, 1.07)	0.27 (34/126)	7

Numbers needed to treat were calculated as $1/|\text{assumed control risk}^(1 - \text{risk ratio})|$, for which the assumed control risk was the pooled event rate in the HP group and outcomes were rounded to the nearest whole number.

Supplemental Table 6a Outcomes of the reversal procedure (1/2)

Study	Group	No. of stomas reversed/constructed (%)	Time interval to reversals	Mortality	Morbidity	Clavien-Dindo	Reoperations	LOS (days)	ICU stay
Randomized controlled trials									
Binda	HP	34/56 (60.7%)	183.5 (121) days	0	8 (23.5%) ^a	n.r.	3 (8.8%)	n.r.	n.r.
	PA	22/34 (64.7%)	161.4 (141) days	0	1 (4.5%) ^a	n.r.	1 (4.5%)	n.r.	n.r.
Bridoux	HP	33/52 (63.5%)	n.r.	1 (3%)	7 (21.2%) ^a	3 (9%) ^b	n.r.	7 (3-22)	n.r.
	PA	32/35 (91.4%)	n.r.	0	4 (12.5%) ^a	1 (3%) ^b	n.r.	5 (3-33)	n.r.
Lambrichts	HP	44/65 (66.7%)	133 (102-208) days	0	Major: 7 (16%) Minor: 6 (14%) Overall: 13 (30%)	n.r.	4 (9%)	5 (4-6)	n.r.
	PA	38/46 (82.6%)	113.5 (80-155) days	0	Major: 1 (3%) Minor: 2 (5%) Overall: 3 (8%)	n.r.	1 (3%)	4 (2.8-5)	n.r.
Oberkofer	HP	15/30 (50%)	Median: 6 months	0	6 (40%) ^d	3 (20%) ^e	n.r.	9 (6-17)	n.r.
	PA	26/32 (81.3%)	Median: 3 months	0	6 (23%) ^d	0 ^e	n.r.	6 (4-10)	n.r.
Observational studies									
Regenet	HP	20/29 (70%)	151 (71.7) days	0	5 (24%) ^a	n.r.	n.r.	n.r.	n.r.
	PA	0/0	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Richter	HP	1/5 (20%)	16 months	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Schilling	HP	32/42 (76.2%)	169 (74) days	n.r.	n.r.	n.r.	n.r.	15.4 (8.4)	0.8 (1.5)
	PA	0/0	n.a.	n.r.	n.r.	n.r.	n.r.	n.a.	n.a.
Trenti	HP	9/33 (27.3%)	76.2 (63) days	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA	3/5 (60%)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Vennix	HP (open)	0.64 12-month stoma-free probability	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	HP (laparoscopic)	0.88 12-month stoma-free probability	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

Study	Group	No. of stomas reversed/constructed (%)	Time interval to reversals	Mortality	Morbidity	Clavien-Dindo	Reoperations	LOS (days)	ICU stay
Wright	PA (open)	1.00 12-month stoma-free probability	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	PA (laparoscopic)	1.00 12-month stoma-free probability	n.a.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	Overall (colorectal)	20/25 (80%)	n.r.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	Overall (general)	20/30 (66.7%)	n.r.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	HP (colorectal)	10/21 (47.6%)	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	HP (general)	22/34 (64.7%)	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	PA (colorectal)	n.r.s.	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	PA (colorectal)	n.r.s.	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	PA (colorectal)	n.r.s.	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.
	PA (colorectal)	n.r.s.	n.r.s.	n.r.	n.r.s.	n.r.	n.r.	n.r.s.	n.r.

Continuous data are median (interquartile range), mean (standard deviation), or mean (range). a = overall morbidity; b = Clavien-Dindo III-V; c = major morbidity defined as surgical reintervention, percutaneous abscess drainage, fascial dehiscence, urosepsis, myocardial infarction, renal failure, and respiratory insufficiency; minor morbidity defined as surgical site infection, postoperative ileus, pneumonia, delirium, urinary tract infection, abscess without drainage, thrombosis, cardiac complications, and overall morbidity defined as major and minor complications combined; d = Clavien-Dindo I-V; e = Clavien-Dindo III-IV, serious complications. HP, Hartmann's procedure; ICU, intensive care unit; LOS, length of stay; n.a., not applicable; n.r., not reported; n.r.s., not reported separately;

Supplemental Table 6b Outcomes of the reversal operation (2/2)

Study	Group	Reversal (n)	Sepsis	Anastomotic leakage	Intra-abdominal abscess	Abcess drainage	SSI	Other infectious complications	Organ dysfunction	Fascial dehiscence	Incisional hernia	Stoma site incisional hernia
Randomized controlled trials												
Binda	HP	34	n.r.	2 (5.9%)	1 (2.9%)	1 (2.9%)	3 (8.8%) deep, 5 (14.7%) superficial	n.r.	n.r.	n.r.	n.r.	n.r.
Bridoux	PA	22	n.r.	1 (4.5%)	0	0	0	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	33	n.r.	0	1 (3%)	1 (3%)	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Lambrichts	PA	32	n.r.	1 (3%)	0	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	44	n.r.	1 (2%)	3 (7%)	3 (7%)	5 (11%)	1 (2%) UTI	0	1 (2%)	n.r.	2 (5%)
Oberkofler	PA	38	n.r.	0	0	0	1 (3%)	0	0	0	n.r.	1 (3%)
	HP	15	1 (6.7%)	2 (13.3%)	n.r.	n.r.	3 (20%)	n.r.	n.r.	n.r.	n.r.	n.r.
Observational studies	PA	26	0	0	n.r.	n.r.	3 (11.5%)	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	9	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Trenti	HP	9	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Trenti	PA	3	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
	HP	3	n.r.	0	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.

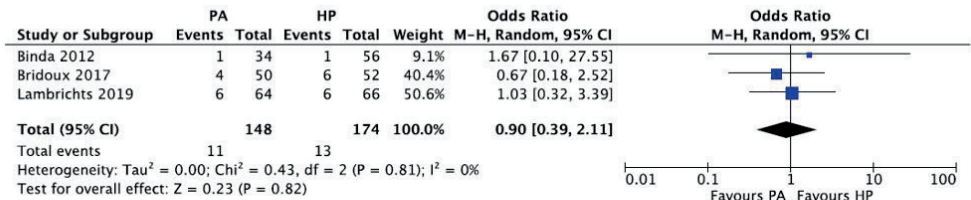
Continuous data are median (interquartile range), mean (standard deviation), or mean (range). a = Complications concerning anastomotic healing, including leakage and anastomotic or presacral abscess. HP, Hartmann's procedure; n.a., not applicable; n.r., not reported; n.r.s., not reported separately; PA, primary anastomosis; SSI, surgical site infection; UTI, urinary tract infection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Binda 2012	+	+	-	?	+	+	?
Bridoux 2017	+	+	-	?	+	+	?
Lambrichts 2019	+	+	-	-	+	+	?
Oberkofler 2012	+	+	-	?	+	+	?

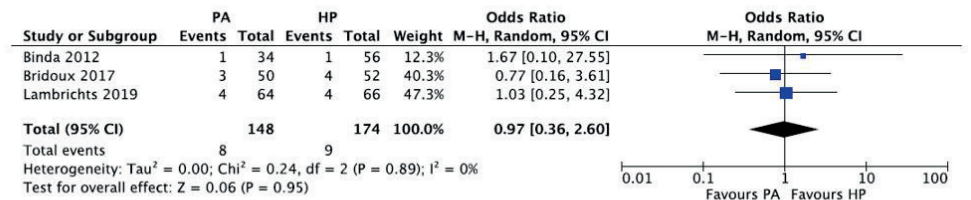
Supplemental Figure 1 Risk of bias

Supplemental Figure 2 Quantitative analyses of:

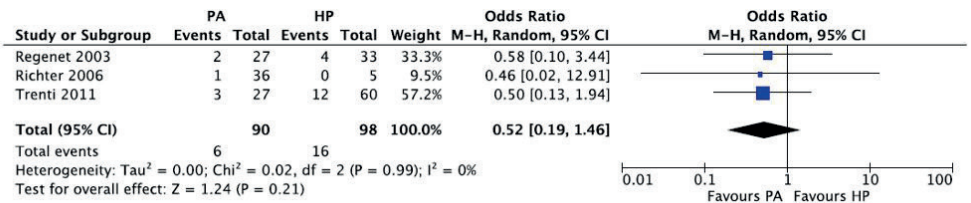
a. Reintervention rates in randomized controlled trials;



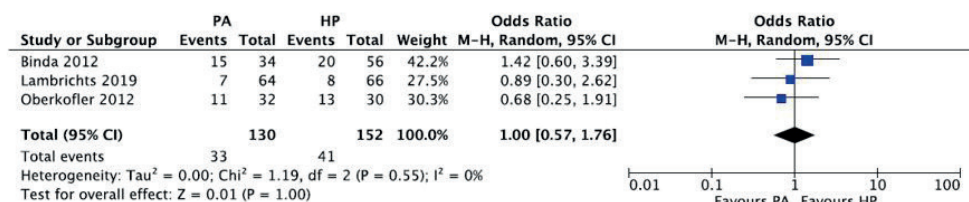
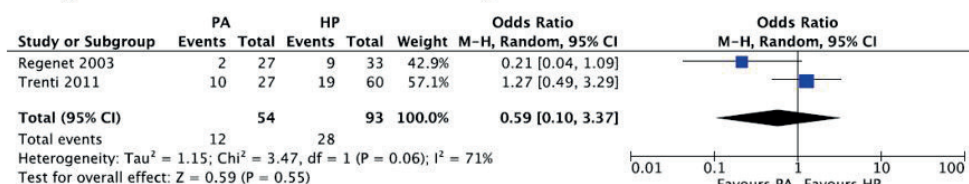
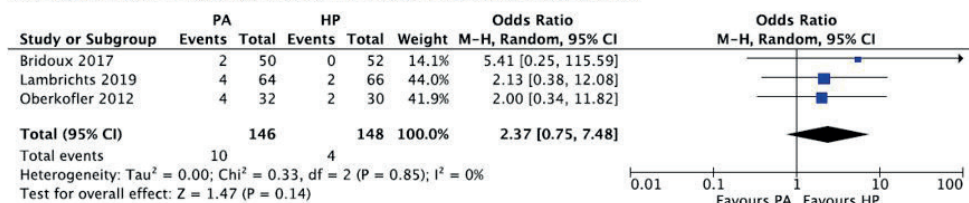
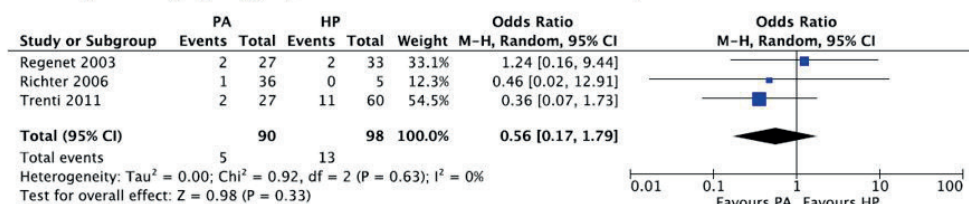
b. Reoperation rates in randomized controlled trials;



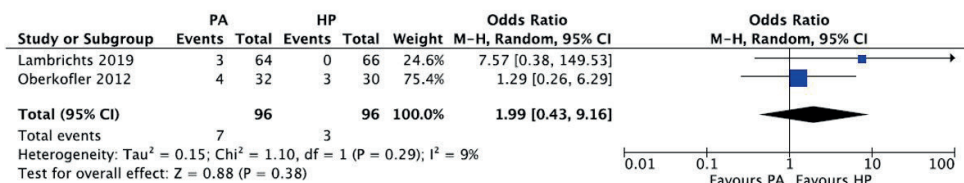
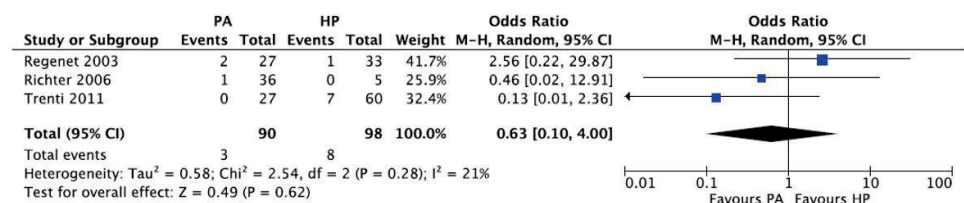
c. Reintervention rates in observational studies.



- a. Reintervention rates in randomized controlled trials;
- b. Reoperation rates in randomized controlled trials;
- c. Reintervention rates in observational studies.

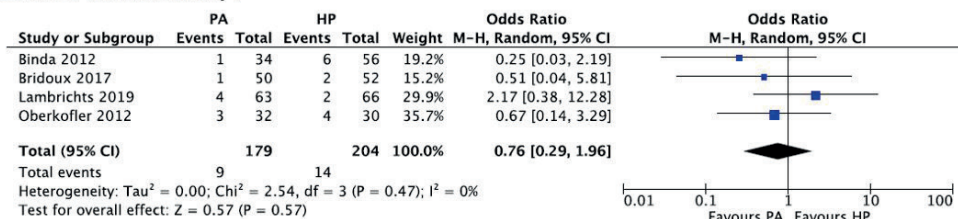
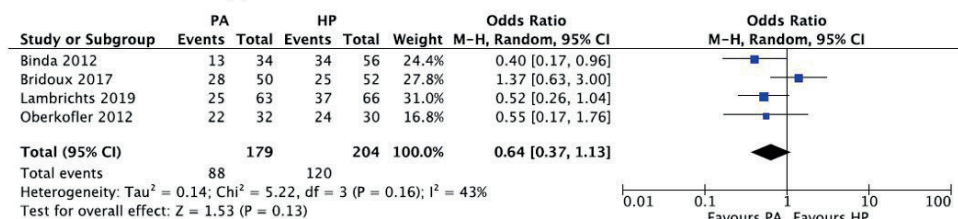
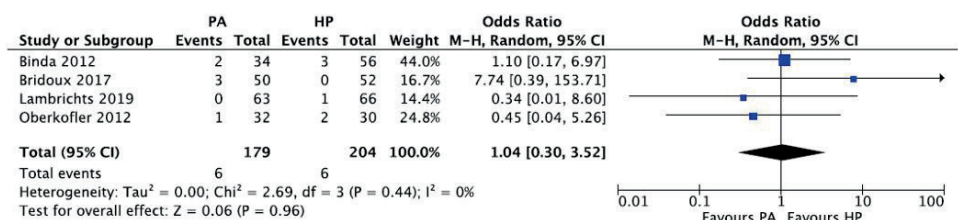
Supplemental Figure 3 Quantitative analyses of:**a. Surgical site infections in randomized controlled trials;****b. Surgical site infections in observational studies;****c. Postoperative (ongoing) sepsis in randomized controlled trials;****d. Postoperative (ongoing) sepsis in randomized controlled trials;**

- Surgical site infections in randomized controlled trials;
- Surgical site infections in observational studies;
- Postoperative (ongoing) sepsis in randomized controlled trials;
- Postoperative (ongoing) sepsis in randomized controlled trials;

e. Fascial dehiscence in randomized controlled trials;**f. Fascial dehiscence in observational studies.**

e. Fascial dehiscence in randomized controlled trials;

f. Fascial dehiscence in observational studies.

Supplemental Figure 4 Quantitative analyses of outcomes after index and reversal procedures combined:**a. Short-term mortality;****b. Short-term morbidity;****c. Anastomotic leakage.**

a. Short-term mortality;

b. Short-term morbidity;

c. Anastomotic leakage.

The first part of the paper discusses the importance of the research and the need for a new approach. It then presents a detailed description of the methodology used in the study, followed by a discussion of the results and their implications. The paper concludes with a summary of the findings and a list of references.

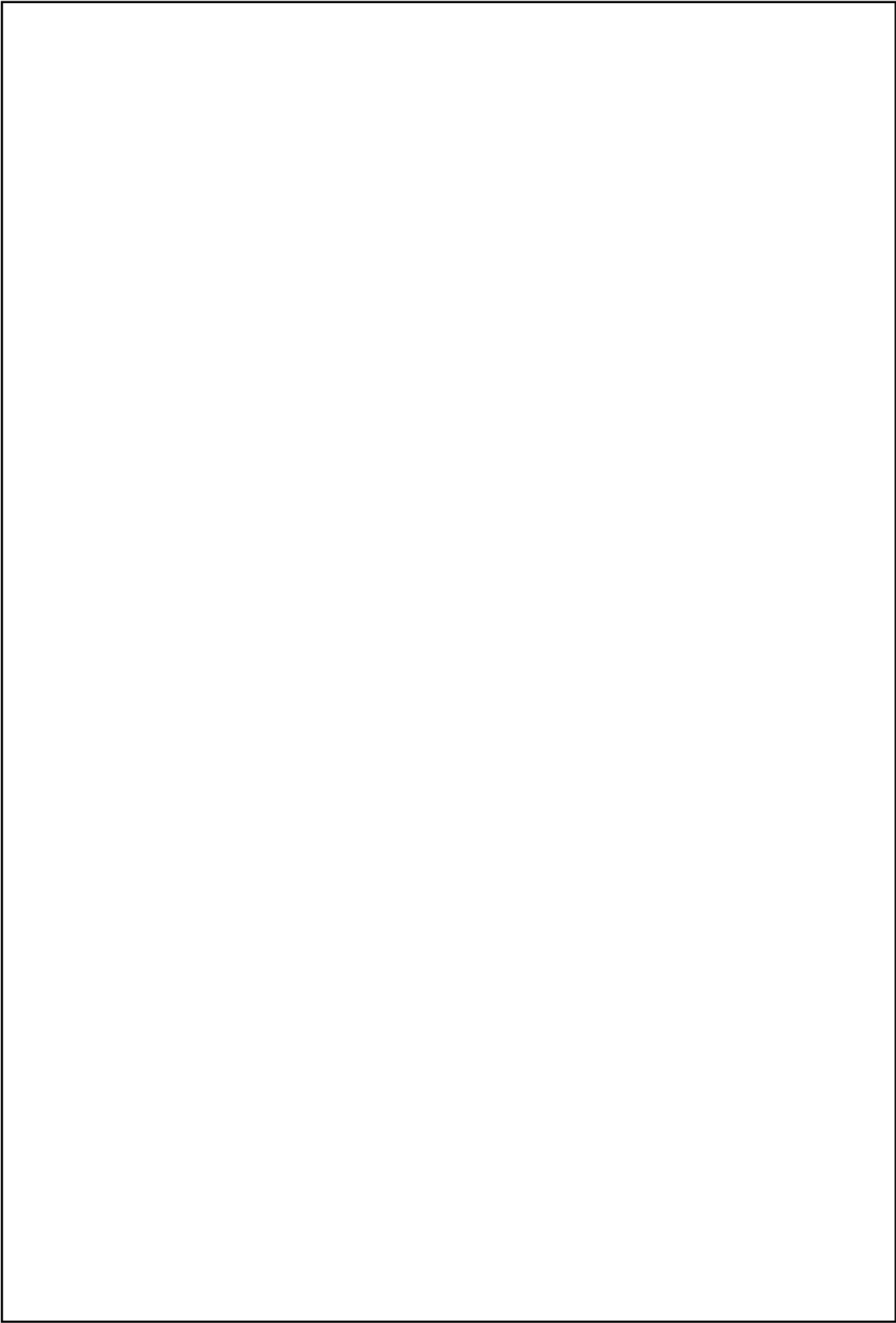
The methodology used in this study is based on a combination of qualitative and quantitative methods. The qualitative methods include interviews with experts in the field, while the quantitative methods involve the use of statistical analysis to test the hypotheses. The results of the study show that there is a significant difference between the two groups, and that the new approach is more effective than the traditional one.

The implications of the study are far-reaching, as they suggest that the new approach could be used in a wide range of contexts. This could lead to improved outcomes in many areas, and it could also help to reduce the costs of many processes. The study also highlights the need for further research in this area, as there are still many questions that need to be answered.

In conclusion, the study has shown that the new approach is more effective than the traditional one, and that it has the potential to improve outcomes in many areas. This is a significant finding, and it suggests that the new approach should be adopted as the standard method for many processes.

Part III

Treatment of (complicated)
diverticulitis: appraisal of the evidence



Chapter 8

The multidisciplinary management of acute complicated diverticulitis

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J.F. Lange, W.A. Bemelman, S. Di Saverio

Inflammatory intestinal diseases 3.2 (2018): 80-90

Abstract***Background***

Acute complicated diverticulitis (ACD) is an important and increasing issue in Western countries that leads to a significant impact and burden for patients, but also for the society due to its effects on hospital costs. In recent years, essential progression has been made regarding the research and implementation of novel or improved treatment strategies for the various disease entities of ACD. Much debated topics in the multidisciplinary approach of patients with ACD, such as the choice for nonoperative treatment options, the role of percutaneous drainage for diverticular abscesses, the role of laparoscopic lavage for perforated diverticulitis with purulent peritonitis and the role of sigmoidectomy with primary anastomosis for patients with perforated diverticulitis, require clinicians to attentively follow and participate in these discussions.

Summary

The aim of this review article is to provide clinicians with a structured overview of the recent literature on the multidisciplinary management of complicated diverticulitis by a panel of experts on the topic. By performing an extensive literature search in the online medical databases MEDLINE (Ovid) and Embase, insights into nonoperative treatment, percutaneous drainage, minimally invasive and open surgical treatment for ACD are provided. Furthermore, a comprehensive algorithm for the treatment of ACD has been developed.

Key messages

Accurate patient evaluation and selection based on patient and disease characteristics is of paramount importance to determine the appropriate treatment strategy for patients with complicated diverticulitis. The presence of an experienced surgeon with advanced skills in laparoscopic emergency colorectal surgery is crucial for the treatment of patients with perforated diverticulitis in order to properly evaluate, select and treat patients suitable for nonoperative or operative treatment with an open or laparoscopic approach.

Introduction

Epidemiology

Diverticulosis coli is a common condition in Western countries with prevalence rates of 5% by the age of 40 years up to 65% when 85 years or older (1). An estimated 15-20% of individuals with diverticulosis coli will develop acute complicated diverticulitis (ACD) in their lifetime (2). The age group of patients with ACD below 50 years of age consists predominantly of men, whereas women seem to be the majority in the group between 50-70 years (1). In recent years, a considerable increase in both uncomplicated and complicated diverticulitis rates have been found, as well as a significant rise in hospital admissions. This has led to a significant increase in associated hospital expenditure of up to 2.4 billion dollars of direct costs annually in the United States (3, 4).

Terminology

The terminology used in the literature regarding diverticulosis coli and diverticular disease is heterogeneous, so uniformity is required in order to correctly interpret and compare results between studies. The general term 'diverticular disease' indicates that diverticulosis has risen to the level of illness (4). In the majority of national and international guidelines acute diverticulitis is further divided into complicated and uncomplicated disease (5). Uncomplicated acute diverticulitis is defined as localized diverticular inflammation without any phlegmon, abscess, perforation, or fistula, whereas acute complicated diverticulitis (ACD) is defined as acute inflamed diverticula giving rise to phlegmon, abscess, fistula or perforation (6). Moreover, recurrent episodes of ACD can lead to late complications such as stenosis or fistula (5).

Classifications of ACD

After Hinchey et al. (7) presented their classification for ACD, various modifications and novel classifications have been proposed to grade the different entities of diverticular disease and ACD in particular (Table 1). The Hansen/Stock clinical classification comprises diverticulosis, as well as uncomplicated and complicated diverticulitis (8). Likewise, Köhler et al. (9) introduced a classification including uncomplicated and recurrent ACD. Both these classifications were based on the clinical severity of the disease, whereas the Hinchey classification was based on operative findings. However, as a result of the increasing role of computed tomography (CT) as diagnostic tool, subcategories could be defined and modified Hinchey classifications were introduced, as well as CT-based classifications, as those by Ambrosetti et al. and Kaiser et al. (10, 11). Modified Hinchey classifications have been introduced by Sher et al. (12) and Wasvary et al. (13), of which the latter is the most widely adopted, focusing not only on perforated disease, but also on mild clinical disease. The number of classifications and the fact that they are based on different clinical, radiological or operative findings has led to discordance in the literature. However, as Klarenbeek et al. (14) stated, a proper classification is necessary to improve communication between doctors, support clinical decision-making, and provide help in prediction of outcomes. Subsequently, they designed a comprehensive grading system that combined existing classifications and differentiates three stages of diverticular disease: uncomplicated, chronic complicated, and acute complicated. For each of these stages clinical characteristics, radiological findings, and

treatment modalities are given (14). More recently, Sartelli et al. (15) have proposed a CT-based classification, with suggested management options, to drive decision-making in nonoperative and operative treatment of ACD. Nevertheless, currently, the modified Hinchey classification (Fig. 1) remains the most widely used classification and is used in several guidelines, and will be further referred to in this review (5, 13).

Diagnosis

In the clinical work-up of ACD it is of paramount importance to diagnose and differentiate patients timely and correctly in order to initiate appropriate management. Moreover, accurate staging of the disease has become increasingly important, since treatment approaches have become less aggressive and more tailored to the stage of diverticulitis (16). The clinical diagnosis of ACD seems to be correct in 43-68% of patients, when only based on symptoms, physical examination and laboratory results (1). External validation of a clinical decision rule has shown that isolated tenderness in the left lower quadrant, C-reactive protein level of >50 mg/L, and absence of vomiting might have predictive value in patients with suspected acute diverticulitis. However, it must be acknowledged that these criteria only identified up to 24% of patients and, therefore, clinical assessment still remains insufficiently precise (17). It is suggested that in these patients imaging might be omitted, but in general, the clinical diagnosis of ACD is not sufficiently accurate and all guidelines recommend radiological evidence to support clinical diagnosis (1, 5). Diagnostic techniques that have been assessed are double-contrast barium enemas, magnetic resonance imaging (MRI), colonoscopy, ultrasound (US), and CT scan. However, double-contrast barium enema is contraindicated in the setting of suspected ACD, due to its low accuracy, high radiation exposure and low patient acceptability (18). MRI has the advantage that contrast is not needed and does not expose the patient to ionizing radiation, but sufficient evidence and accuracy data are still lacking (19). Furthermore, in many hospitals, availability of MRI in the emergency department is limited (18). Colonoscopy is not recommended in the acute phase, because of potential difficulties, such as incomplete bowel preparation, bowel stenosis, and the risk of perforation and bleeding (18, 20). US and CT are comparable in diagnosing diverticulitis and superior to other modalities, with a sensitivity of 92% vs. 94% and specificity of 90% vs. 99%, respectively (19, 21). Nowadays, CT is the established method of choice when compared to US and most guidelines agree on the high accuracy and other advantages of CT (5, 22). Andeweg et al. (19) published a step-up approach in which CT is performed after an inconclusive or negative graded compression US. Nevertheless, CT is recommended for severe peritonitis, since it is superior to US in providing an alternative diagnosis and detecting complicated disease (5, 16).

Nonoperative treatment

In past decades, ACD management has moved towards a more nonoperative approach, by virtue of significant progression in critical care medicine, interventional radiological techniques, antibiotic treatment, parenteral nutrition, and diagnostic accuracy of CT (23). Results of the DIABOLO trial by Daniels et al. (24) indicate that observational treatment without antibiotics did not prolong recovery and can be considered appropriate in Hinchey Ia and Ib patients. Moreover, Stam et al. (25) concluded that an unrestricted

diet is safe in this patient population. Nowadays, the goal of surgical care for ACD, is to convert an emergent surgical situation into an elective situation, by means of aggressive, supportive medical care (23, 26). Despite this important change in treatment strategy, literature on this topic is scarce, especially with concern to more complex cases of ACD. Consequently, optimal treatment strategies remain controversial, notably in patients presenting with extraluminal air (27). A considerable overall success rate of 91% for a nonoperative approach in patients with extraluminal air was reported by Dharmajaran et al. (23), who managed patients in a monitored setting, with intravenous (IV) fluids, broad-spectrum IV antibiotics, and bowel rest, according to local protocol. If possible, percutaneous drainage (PCD) was advised in patients with an abscess larger than 4 cm, indicating the importance of a multidisciplinary management with involvement of interventional radiologists. Sallinen et al. (27) reported a 62% success rate in patients with distant intraperitoneal air, although this rate increased to 86% when patients with abundant distant intraperitoneal air or fluid in the recto-vesical or recto-uterine pouch were excluded. In the World Society of Emergency Surgery (WSES) guidelines (28) it is stated that patients with CT findings of pericolic air or small fluid collection should be managed by antimicrobial therapy. Furthermore, it is articulated that nonoperative treatment might be an option in selected patients with distant air, but without diffuse fluid on CT. However, clearly, surgery is still indicated in case of failure of this approach. Initial choice of antibiotic regimen should be empirical and therefore partly depends on presumable pathogens involved, as well as local resistance profiles and other risk factors for resistance patterns (29). Additional CT imaging is advised in patients with persistent signs of intra-abdominal infection after 4-6 days, or in case of recurrent evidence of infection (15). Although the reported results seem to indicate that nonoperative management is a viable option, even in patients with extraluminal air, a careful case-by-case decision should still be made, with attention to the patient's clinical state (30, 31). Evidently, nonoperative management is contraindicated in case of hemodynamic instability, generalized peritonitis, diffuse free air and fluid on CT, immunosuppression, or comorbidities that hinder the resolution of sepsis (23).

Percutaneous drainage

An important group of patients with ACD that can initially be treated non-surgically are patients with diverticular abscess formation (Hinchey IIa and IIb). This peri- or paracolic abscess formation occurs in 15-40% of ACD cases and is caused by bacteria and inflammatory cells spreading into the mesocolon and peritoneal cavity (32). Treatment choice in the acute setting depends on clinical presentation, size and location of the abscess, as well as the amenability for PCD (32). At present, no definite consensus has been reached on the optimal approach for this patient group, due to the lack of high-quality research (1). Definitions of a large abscess vary from 2 to 5 cm throughout literature, but the cut-off value of >4-5 cm is generally used in publications and guidelines (1, 5, 28, 32). However, as supported by several international guidelines, small mesocolic abscesses can be treated with antibiotics alone, whereas larger mesocolic or pelvic abscesses require PCD (5). In case of small abscesses (<4-5cm) bowel rest, pain control and IV antibiotics are advised. In the absence of clinical trials comparing antibiotic regimens, recommendations on specific agents or treatment duration cannot be made (33). Nevertheless, broad-spectrum, IV antibiotics, covering anaerobic and

gram-negative bacteria, are considered as essential component of successful nonoperative treatment (33, 34). In choice of imaging modality, ultrasound (US) guided drainage has the benefit of easy handling, low costs and avoidance of ionizing radiation. However, despite these benefits, the US-guided method might be predominantly convenient in superficial abscesses, partly because the air acoustic barrier of bowel loops can limit the abdominal approach (35). CT-guided PCD is considered to be the preferred and the most effective method for detection and interventional guidance of abscesses drainage in the abdomen and pelvis, because of the anatomic detail and localization related to nearby vital structures (35, 36). Several access routes for interventional radiological drainage exist such as the transabdominal approach (anterior or lateral) and transgluteal approach. The latter approach can be considered as option for deep pelvic abscesses and requires CT-guidance (35, 36). Furthermore, endocavitary (e.g. transrectal) approaches might be suitable for more complex, deep pelvic collections (35, 36). Endoscopic transluminal abscess drainage has been proposed as a treatment option for diverticular abscesses, however no strong evidence exists on this topic (37-40).

Both the direct trocar technique and the Seldinger technique can be used during the procedure, from which the trocar technique seems faster and better suited for large fluid collections, whereas the Seldinger technique is more time-consuming and suitable for complex pelvic collections (35, 36). Size of the catheter depends on the viscosity of the fluid and should not be too small to avoid kinking and clogging. Moreover, daily flushing of the catheter is recommended to maintain effective drainage (35, 36). Timing of catheter removal can be based on clinical and imaging criteria (35). If resolution of the abscess is not reached and the patient has no clinical improvement, repeated CT and further drainage or catheter repositioning might be indicated, and eventually necessitate surgery (28, 35, 41). Laparoscopic drainage has a limited role in the treatment of diverticular abscesses, but may be considered in case of a large abscess that is not amenable for PCD (42).

In their systematic review, Gregersen et al. (32) found that nonoperative treatment failure rate, regardless of treatment choice, was 19-21% for both PCD and antibiotic treatment, with failure defined as emergency surgery, readmission or mortality within 30 days from initial treatment, residual abscess, or persistent symptoms. However, these results need to be carefully interpreted, because treatment groups may primarily reflect disease severity (indication/selection bias), since antibiotics were mainly used for smaller and primarily Hinchey Ib abscesses, and PCD for larger, Hinchey II abscesses. Several reasons for treatment failure of PCD have been identified, such as a multiloculated or pelvic abscess occurrence, or patients with significant comorbidities (32, 41). Jalouta et al. (43) found a 77% recurrence-free survival after nonoperative treatment. Overall, a pooled recurrence rate of 25.5% is observed in the nonoperative treatment group, consisting of patients treated with antibiotics and/or PCD, whereas PCD and antibiotics alone have a pooled average recurrence rate of 15.9% and 22.2% respectively (32). However, the overall recurrence can get as high as 68%, especially in risk groups of patients with abscesses larger than >5 cm or at pelvic or distant locations (32, 34). Moreover, Gregersen et al. (32) found a weighted average of 4.8% (median 1.3%, range

0-18.2%) of acute or urgent surgery due to recurrence following successful nonoperative treatment.

No clear consensus exists on follow-up after the nonoperative treatment of diverticular abscesses, although the WSES guideline advises early colonoscopic evaluation (4-6 weeks) (28). More importantly, the role and necessity of elective surgery is still debated. Although no strong evidence exists, from their systematic review, Lamb et al. (34) have concluded that abscess formation is associated with a high probability of resectional surgery at follow-up, whilst nonoperative management may evidently result in recurrent diverticular disease. Therefore, the choice for elective surgery should be made on a case-by-case basis, until future research clarifies how to select patients for whom elective surgery might be indicated (5, 34).

Operative treatment

Minimally invasive operative treatment

Although the open approach is still the most common in operative treatment of ACD, encouraging data on the feasibility and advantages of laparoscopic treatment have been published and the minimally invasive approach in the management of ACD has been included in the EAES, Dutch, and WSES guidelines (5, 28, 44).

Patients needing operative treatment of ACD are commonly critical and their clinical status might be severely impaired by sepsis. In these patients, laparotomy often leads to high morbidity rates (e.g. wound infection, pneumonia, renal failure, adhesions, and incisional hernias). Therefore, especially in these acute patients, the minimally invasive surgical treatment might significantly decrease postoperative complication rates and allow a faster recovery, as compared to the open approach. However, to proceed to a laparoscopic treatment of ACD, it is of paramount importance that the patient is hemodynamically stable and has no absolute contraindications to pneumoperitoneum. Either severely inflamed tissues in perforated ACD, or severe bowel distention in obstructing ACD, make the surgical procedure technically demanding and the presence of an acute care surgeon with advanced laparoscopic colorectal skills is recommended.

According to the patient's status, available surgical expertise and extent and severity of underlying disease, the surgical treatment of ACD can be either non-resectional or resectional.

Laparoscopic non-resectional treatment

Laparoscopic lavage (LL) has first been described in 1996, as a minimally invasive technique to avoid resection in perforated diverticulitis with purulent peritonitis (45, 46). Since then, the technique has not gained a wide acceptance and, up to date, three randomized controlled trials (RCT) comparing LL to sigmoidectomy have been published (47-49). Interestingly, their conclusions did not agree and the strong debate raised from these conflicting results led seven meta-analyses to be published over the last two years (50-56). Some authors claimed selection biases in the RCTs (57) or

methodological flaws in the meta-analyses, since opposite conclusions on the 30-day and 90-day reoperation risk were reported in the meta-analyses(58). Despite its increased incidence of postoperative abscesses and PCD, LL still appears to be faster and leading to a faster recovery. No indisputable differences in terms of postoperative short- and long-term mortality, morbidity and stoma presence at 12 months seem to be present (50-56). LL might, however, be more cost-effective as compared to resection (59, 60).

The main factor related to failure or success of LL is the grade of experience of the operator (61). The intra-operative distinction between Hinchey III and IV is not always obvious and experience and technical skill are essential features for effective irrigation, drainage and, most importantly, reliably ruling out free perforation or perforated cancer (61). An experienced surgeon is better able to distinguish between purulent and fecal peritonitis and is more likely to be able to identify the perforation, which mostly is on the mesenteric side of the sigmoid, surrounded by dense inflammatory tissue, and therefore not easily accessible or visible. Intraoperative endoscopy or insufflation of CO₂ in the rectum might be helpful to discriminate between a sealed or open perforation. Furthermore, since purulent peritonitis is the consequence of transient peritoneal contamination, with a sealed perforation at the time of the operation, the main aim of LL might not be to control the source of infection, but to clean the peritoneal cavity, reduce microbial contamination and the consequent release of inflammatory factors, in order to improve sepsis treatment. In this view, the peritoneal washout must be as complete and careful as possible, including thorough cleaning of all four quadrants' recesses and placement of abdominal drains deep in the Douglas' and Morison's pouches. Inexperienced surgeons might be less competent to correctly perform these procedural steps, potentially leading to an increased rate of persistent sepsis or intra-abdominal collections. LL may represent a valuable option for the management of perforated diverticulitis with purulent peritonitis, however, the risk of failure, early reintervention, perforated carcinoma and diverticulitis recurrence need to be balanced against the risk of sigmoidectomy, and potential stoma formation and closure (49, 62). Therefore, correct patient evaluation, performed by an experienced surgeon, with advanced skills in laparoscopic emergency colorectal surgery, is crucial for the selection and treatment of stable, young and fit patients, without an overt perforation.

Laparoscopic resectional treatment

The literature on emergency laparoscopic Hartmann's procedure (HP) or sigmoidectomy with primary anastomosis (PA) for ACD is still scant. Several small retrospective cohort studies and case series have been published, but no RCTs comparing the laparoscopic and open approach in the acute setting exist (63), mostly because of concerns about the clinical characteristics of ACD that, potentially, negatively affects outcomes of the laparoscopic approach. In the acute setting, the distended bowel, inflammatory dense adhesions, and the contamination of the abdominal cavity caused by perforated ACD often raise concerns on the safety and feasibility of the approach. Moreover, the severely inflamed tissues make the procedure remarkably more challenging if compared to the elective sigmoid colectomy (Fig. 2), with loss of anatomical planes and consequent increased risk of bleeding and ureteric injuries. Because of these technical demands, it is

therefore advisable to consider these procedures only in the presence of an experienced surgeon, who is highly skilled in emergency laparoscopic colorectal surgery.

Small retrospective series have demonstrated emergency laparoscopic sigmoidectomy in ACD to be safe and feasible, with significant advantages in terms of low conversion, reintervention, morbidity, and mortality rates, as well as faster recovery, and higher stoma reversal rates (64). Although the published studies are limited by their small size, heterogeneity of participants and outcome variables, obvious selection bias, and lack of open control group, it is still stated that the approach is feasible in selected patients and experienced hands (64), as was also concluded in a recent propensity-score matched analysis (65). Furthermore, the benefit of laparoscopic HP might be a decrease in abdominal wall complications, such as incisional hernias (65). Subsequently, this might lead to higher rates of stoma reversal in the follow-up of these patients.

In selected cases, it can be decided to perform a sigmoidectomy with PA, with or without defunctioning loop-ileostomy, depending on patient's age, comorbidities and clinical condition. Furthermore, the intraoperative quality of colonic tissue and edges is of importance (e.g. not ischemic), and it is important that these can be joined without tension, making routine splenic flexure mobilization highly recommendable. The role of defunctioning loop-ileostomy can be debated in emergency procedures since the colon has not been prepared, even though an intraoperative colonic antegrade enema through the appendicular orifice may be performed after the resection and PA have been performed. The largest reported series of emergency laparoscopic anterior resection and PA for complicated diverticular disease is the one by Titu et al. (66) including 50 cases, with an anastomotic leak rate of 8%. The retrospective comparative cohort study by Letarte et al. (67) included 103 emergency colonic resections and primary anastomosis (37 laparoscopic vs. 66 open) for acute complicated diverticulitis, with no significant difference in the anastomotic leak rate. Overall, no mortality and significantly better postoperative outcomes were found in the laparoscopic group, in terms of less frequent prolonged ileus (12.8% vs 32%), shorter time to oral intake (3 vs. 6 days) and shorter LOS (5 vs. 8 days) (67). Moreover, Vennix et al. (63) performed a systematic review of four case series and one cohort study, in which a total of 104 patients underwent emergency laparoscopic resection for perforated diverticulitis (84 Hartmann, 20 primary anastomoses). Mean operating time varied between 115 and 200 minutes, conversion rate varied from zero up to 19%, mean hospital stay ranged between 6-16 days, surgical reintervention was necessary in two patients, no anastomotic leak was reported, and three patients died postoperatively. In highly selected and fit patients, the presence of fecal gross contamination, with peritonitis lasting less than 12-24 hours, might not be an absolute contraindication to laparoscopic resection and PA, although data on this topic are limited (68). Accordingly, the essential aspects of laparoscopic resectional treatment are accurate patient evaluation, selection and treatment by experienced laparoscopic colorectal surgeons.

Before embarking in challenging laparoscopic emergency colorectal procedures, expertise in acute care, emergency and colorectal surgery, as well as minimally invasive expertise (e.g. having completed a laparoscopic fellowship) are required. In absence

of an experienced emergency colorectal laparoscopic surgeon, advanced laparoscopic procedures should not be performed and open procedures are advised outside centers of excellence (61, 69-72).

Open operative treatment

Although laparoscopic resectional treatment has gained increasing attention and promising results have been published, general peritonitis is often still regarded as a contraindication for the laparoscopic approach, especially when fecal. Moreover, concerns have been raised on the risk of damage to the vulnerable and distended small bowel, as well as the hypothetical risk of increased bacteraemia and hypercapnia, caused by pneumoperitoneum (63, 65). Despite the fact that there is no strong evidence proving or disproving these concerns, laparotomy and HP are still the most commonly used procedures (28, 63). The role of sigmoid resection with PA vs. HP has been discussed in several studies (73, 74). Potentially, PA, with or without construction of a temporary loop ileostomy, has the major benefit of avoiding an end colostomy, and the significant risks associated with Hartmann's reversal. In their systematic review, Constantinides et al. (73) found favorable results regarding mortality for PA as compared to HP, however, they correctly indicated the considerable risk of selection bias in the studies under review, due to their retrospective design. To reduce this bias, introduced by performing PA in more favorable subjects, prospective randomized studies were soon designed and conducted. As stated by the authors, from the prematurely terminated trial by Binda et al. (75) no conclusions could be drawn on treatment preference, although they included a total of 90 patients (15% of calculated sample size) of which 15 patients (16.7%) had Hinchey IV. Furthermore, Oberkofler et al. (76) published results favoring PA with diverting ileostomy over HP in a total of 62 patients (30 HP vs. 32 PA). In the HP and PA group, respectively, postoperative outcomes were not significantly different (mortality 13% vs 9% and morbidity 67% vs 75%). Nevertheless, the stoma reversal rate was higher and operating time, hospital stay, and in-hospital costs were significantly reduced in patients who underwent PA. Currently, results of the DIVA-arm of the LADIES trial are awaited, in order to further elucidate this important and much discussed surgical topic (77). Despite the absence of strong evidence, HP is advised for critically ill patients or patients with multiple comorbidities, whereas PA, with or without a diverting loop-ileostomy, is considered safe or even preferable for hemodynamically stable patients with Hinchey III and IV diverticulitis or after failed nonoperative treatment of ACD (Hinchey I-III) (1, 5, 28).

Conclusions

Diverticulitis is an important and increasing problem in Western countries, leading to an increase in hospital admissions and expenditure. Therefore, the use of uniform and comprehensive terminology and disease classification is necessary in order to improve diagnostics, subsequent treatment choices, and future research related to ACD. Contrast CT scan is the gold standard for the diagnosis of ACD. Due to advances in critical care medicine and interventional radiological techniques nonoperative treatment strategies might be viable even in highly selected patients with extraluminal air. In case of abscess

formation, size and location of abscess should, apart from patient characteristics, be taken into consideration before performing PCD. In selected cases and in presence of an experienced emergency colorectal laparoscopic surgeon, minimally-invasive operative management of ACD is feasible and has multiple advantages. Benefits and risks of LL should, evidently, be balanced with those of resectional treatment. HP (open or laparoscopic) is the most common resectional treatment in case of ACD with peritonitis, failed nonoperative management of ACD or acute large bowel obstruction resulting from diverticular disease. A benefit of laparoscopic HP might be a decrease in abdominal wall complications, such as incisional hernias, with a subsequently higher rate of stoma reversal. In case of resectional treatment (open or laparoscopic), a PA can be performed, with or without defunctioning loop-ileostomy, depending on patient's age, comorbidities and clinical condition, as well as intraoperative findings and quality of colonic tissue. According to the modified Hinchey classification of ACD, a comprehensive algorithm for the management of ACD has been developed (Fig. 3).

In conclusion, accurate patient evaluation based on clinical and disease characteristics is of paramount importance to determine the appropriate treatment strategy of ACD. Future research should aim to provide data supporting accurate case-by-case evaluation and decision-making in order to improve the various mentioned aspects of the multidisciplinary treatment of complicated diverticulitis.

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Tables

Table 1 Overview of classifications for diverticular disease

Clinical findings			CT findings				
Hinchey et al. [7]	Sher et al. [12]	Wasvary et al. [13]	Hansen et al. [8]	Köhler et al. [9]	Kaiser et al. [10]	Ambrosetti et al. [11]	Sartelli et al. [15]
Uncomplicated disease							
-	-	0. Mild clinical diverticulitis	0. Diverticulosis I. Acute uncomplicated diverticulitis	Symptomatic uncomplicated	-	-	Diverticula, thickening of the wall, increased density of the pericolic fat
Complicated disease							
I. Pericolic abscess or phlegmon	I. Pericolic abscess	Ia. Confined pericolic inflammation or phlegmon Ib. Pericolic or mesocolic abscess	II. Acute complicated diverticulitis IIa. Phlegmon, peridiverticulitis IIb. Abscess, sealed perforation IIc. Free perforation	Complicated disease: – Hemorrhage – Abscess – Phlegmon – Fistula – Stricture – Perforation – Purulent and fecal peritonitis – Small bowel obstruction due to post-inflammatory adhesions	0. Diverticuli +/- colonic wall thickening	Moderate diverticulitis: – Localized sigmoid wall thickening (<5 mm) – Pericolic fat stranding	Ia. Pericolic air bubbles or little pericolic fluid without abscess Ib. Abscess ≤4 cm
II. Pelvic, intra-abdominal or retroperitoneal abscess	IIa. Distant abscess amenable to percutaneous drainage IIb. Complex abscess associated with fistula	II. Pelvic, distant intra-abdominal or retroperitoneal abscess			Colonic wall thickening with pericolic soft tissue changes: Ia. Changes + pericolic or mesocolic abscess Ib. Changes + distant abscess (generally deep in the pelvis or interloop regions)	Severe diverticulitis: – Abscess – Extraluminal air – Extraluminal contrast	IIa. Abscess >4 cm IIb. Distant air (>5 cm from inflamed bowel segment)

Clinical findings			CT findings				
Hinchey et al. [7]	Sher et al. [12]	Wäsvary et al. [13]	Hansen et al. [8]	Köhler et al. [9]	Kaiser et al. [10]	Ambrosetti et al. [11]	Sartelli et al. [15]
III. Generalized purulent peritonitis	III. Generalized purulent peritonitis	III. Generalized purulent peritonitis			III. Free gas associated with localized or generalized ascites and possible peritoneal wall thickening		III. Diffuse fluid without distant free air (no hole in colon)
IV. Generalized fecal peritonitis	IV. Fecal peritonitis	IV. Generalized fecal peritonitis			IV. Same findings as III		IV. Diffuse fluid with distant free air (persistent hole in colon)
Recurrent disease							
-	-	-	III. Chronic recurrent diverticulitis	Recurrent symptomatic disease	-	-	-

Figures

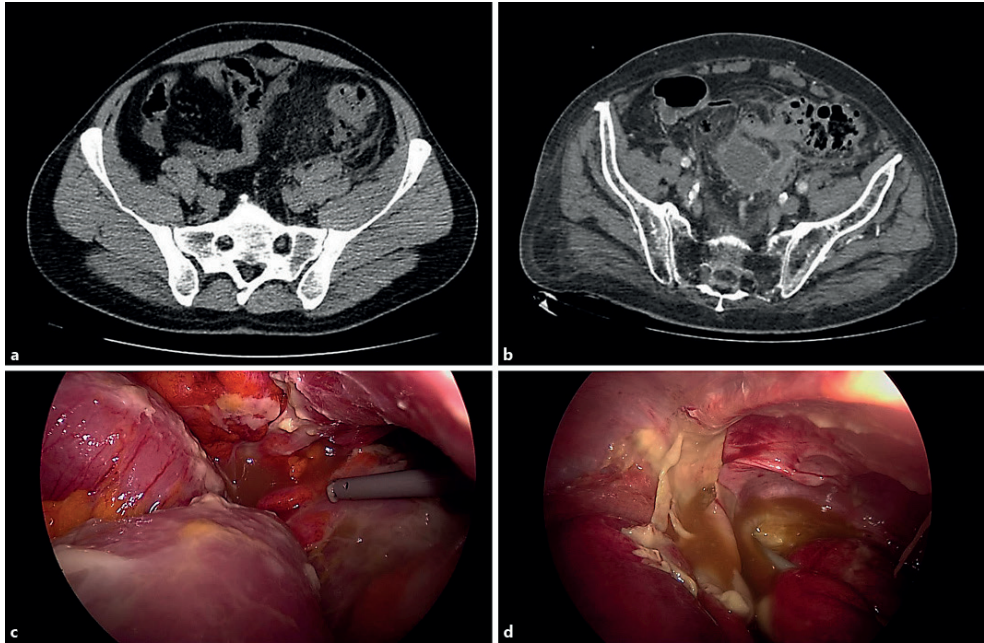


Figure 1 Radiological and clinical images of the modified Hinchey classification. Hinchey Ib: CT image of pericolic abscess (a); Hinchey II: CT image of pelvic abscess (b); Hinchey III: intraoperative image of purulent peritonitis (c); Hinchey IV: intraoperative image of fecal peritonitis (d). Pictures provided by Dr. Salomone Di Saverio, MD, FACS, FRCS; patients gave permission to publish.

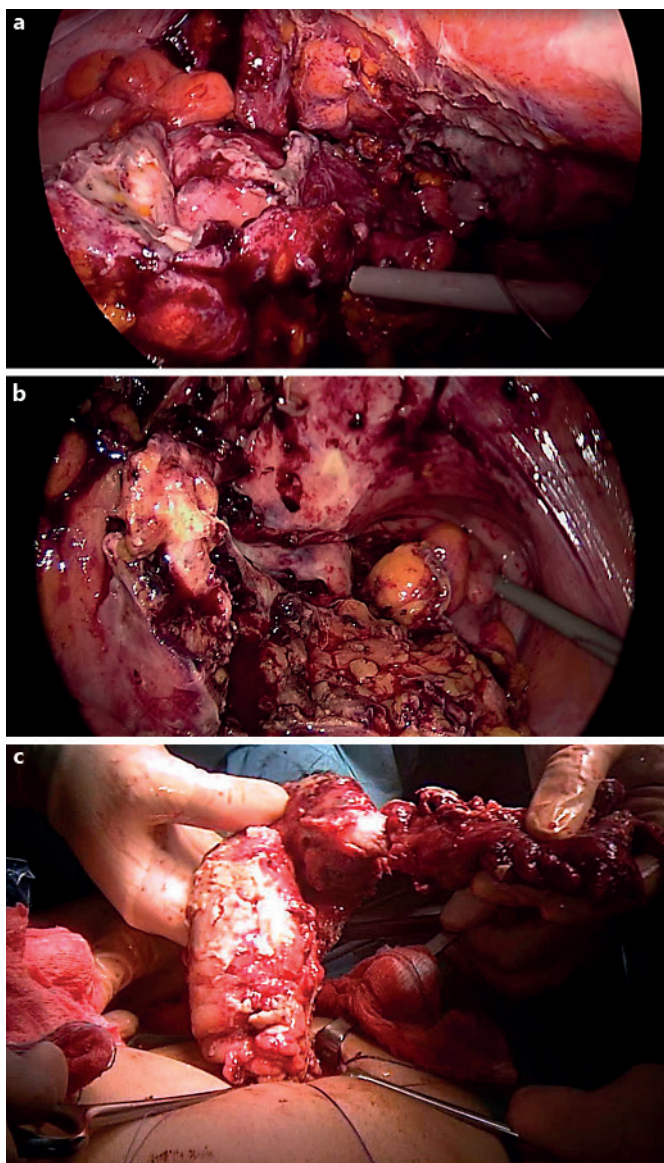


Figure 2 Operative steps of laparoscopic HP for ACD. After the inflamed and thickened sigmoid mesocolon is dissected (a), the sigmoid colon is mobilized and the distal intracorporeal stapled resection is performed (b). The specimen is extracted through the colostomy site avoiding any laparotomy (c) and therefore reducing the risk of wound infection and incisional hernia. Operative pictures provided by Dr. Salomone Di Saverio, MD, FACS, FRCS; the patient gave permission to publish.

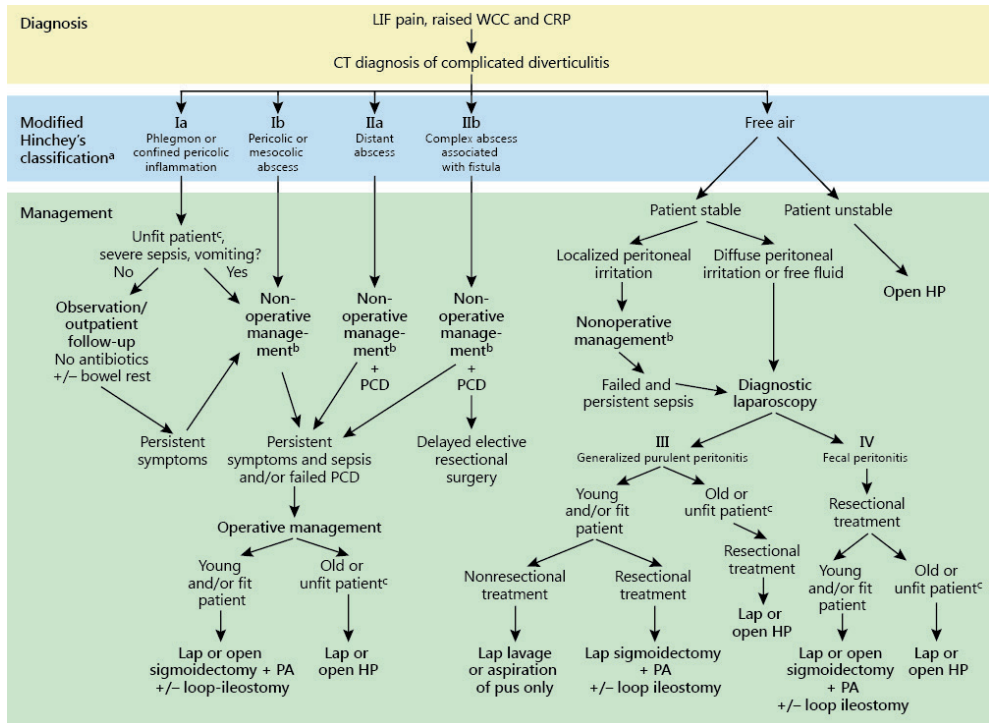
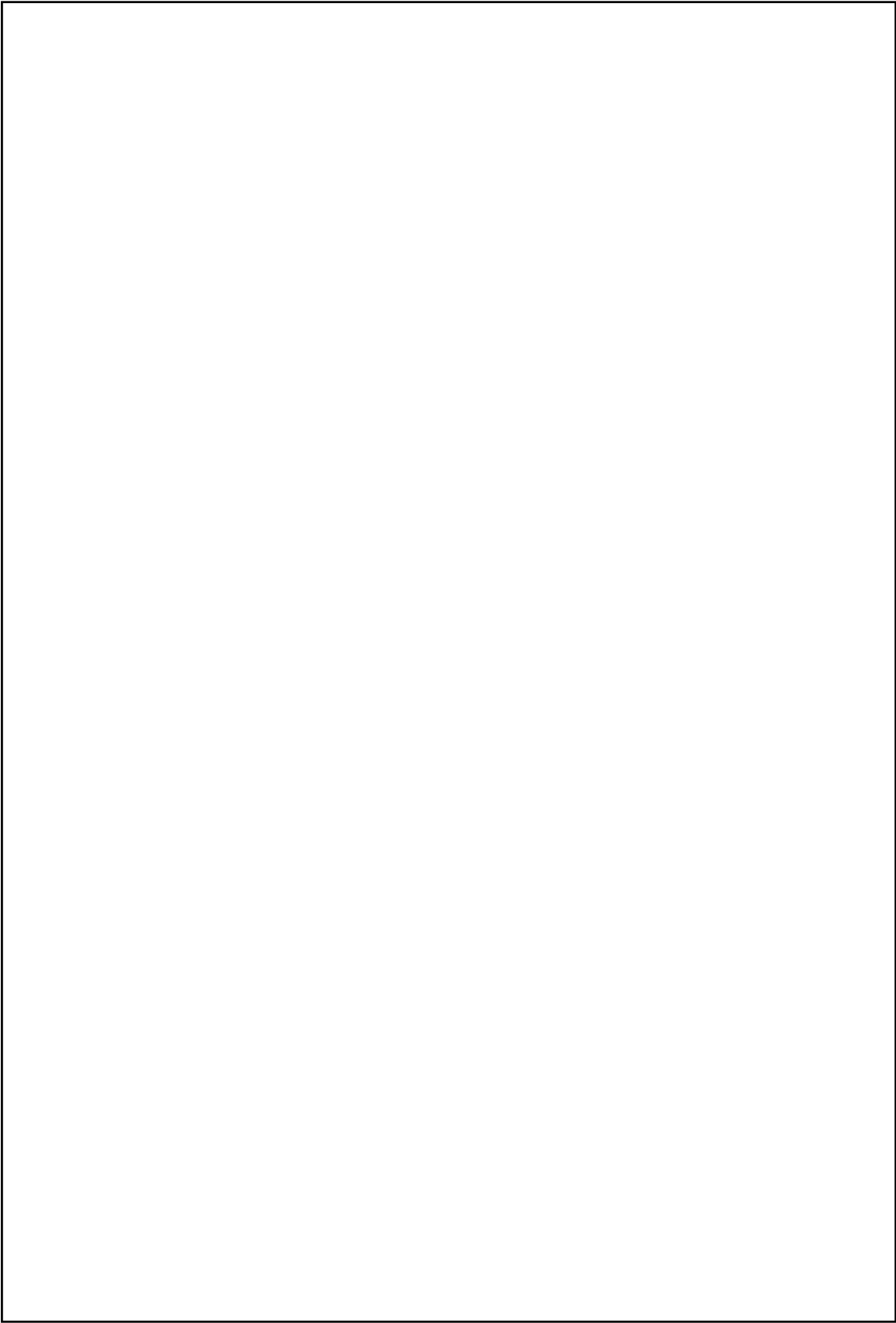


Figure 3 Proposed algorithm for the multidisciplinary management of ACD. PCD, percutaneous drainage; HP, Hartmann's procedure; PA, primary anastomosis. ^a According to Waswary et al. [13] and Sher et al. [12]. ^b Broad-spectrum IV antibiotics and bowel rest. ^c Immunosuppressed, diabetes, chemotherapy, multiple comorbidities.



Chapter 9

European Society of Coloproctology: Guidelines for the Management of Diverticular Disease of the Colon

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Colorectal Disease (June 2020)

Abstract

Aim

The goal of this European Society of Coloproctology (ESCP) guideline project is to give an overview of the existing evidence on the management of diverticular disease, primarily as a guidance to surgeons.

Methods

The guideline was developed during several working phases including three voting rounds and one consensus meeting. The two project leads (JKS and EA) appointed by the ESCP guideline committee together with one member of the guideline committee (WB) agreed on the methodology, decided on six themes for working groups (WGs) and drafted a list of research questions. Senior WG members, mostly colorectal surgeons within the ESCP, were invited based on publication records and geographical aspects. Other specialties were included in the WGs where relevant. In addition, one trainee or PhD fellow was invited in each WG. All six WGs revised the research questions if necessary, did a literature search, created evidence tables where feasible, and drafted supporting text to each research question and statement. The text and statement proposals from each WG were arranged as one document by the first and last authors before online voting by all authors in two rounds. For the second voting ESCP national representatives were also invited. More than 90% agreement was considered a consensus. The final phrasing of the statements with < 90% agreement was discussed in a consensus meeting at the ESCP annual meeting in Vienna in September 2019. Thereafter, the first and the last author drafted the final text of the guideline and circulated it for final approval and for a third and final online voting of rephrased statements.

Results

This guideline contains 38 evidence based consensus statements on the management of diverticular disease.

Conclusion

This international, multidisciplinary guideline provides an up to date summary of the current knowledge of the management of diverticular disease as a guidance for clinicians and patients.

Introduction

There are currently several national guidelines available from member countries of the European Society of Coloproctology (ESCP) on the management of diverticular disease, some of which are not updated (1-7). The guidelines committee of the ESCP decided in 2017 to develop a pan-European guideline for the management of diverticular disease, acknowledging that it will be a compromise of different national guidelines and different accessibilities to healthcare and medical procedures in different healthcare systems.

Method

Two project leads (JKS and EA) were appointed by the guideline committee at the annual ESCP meeting in 2017. Together with a representative from the ESCP guidelines committee (WB), they assembled a team of ESCP and United European Gastroenterology members divided into six work groups (WGs). All WGs comprised a group leader, up to three researchers and a surgical resident who were invited personally to participate by the project leaders. Senior group members were specialists in colorectal surgery, gastroenterology or radiology and were considered based on their scientific contribution in the field. Consideration was taken to ascertain that there was a balanced contribution of the different nationalities within each WG. The groups covered six topics: WG I, Aetiology, follow-up including risk for cancer; WG II, Imaging, indication and classifications, initial evaluation of diverticulitis and imaging; WG III, Nonsurgical management of diverticulitis and dietary recommendations; WG IV, Emergency surgery for acute diverticulitis; WG V, Elective surgery for diverticulitis; WG VI, Technical considerations, special considerations. For all six WGs, research questions were formulated and subsequently revised until all members of the WGs agreed. Each WG conducted their literature research and drafted statements and supporting documentation to their research questions.

Search methods and manuscript selection

Based on the research questions a literature search was performed by the individual WGs. The literature searches were performed using MEDLINE/PubMed/ISI/Scopus and the Cochrane database between July and September of 2018.

Study inclusion criteria were systematic reviews, randomized clinical trials, cohort studies and case series on the subject of colonic diverticulosis and diverticulitis. The trainee or PhD candidate in each research group performed an evaluation of the quality of evidence and created evidence tables with structured summaries for each relevant included article (supplements 1–6; available online). The level of evidence for each recommendation was graded according to the levels of evidence published by the Oxford Centre for Evidence-Based Medicine 2011(8).

The drafting of supporting text and statements

All statements and the initial supporting text were presented at a face to face meeting of the entire team at the ESCP annual meeting in Nice in September 2018. The content

and the strength of each statement and recommendation were reviewed. All statements were then revised to meet the changes requested. A first voting round with all WG members was conducted online in February 2019. After the voting, all statements and the supporting text were revised by the WGs taking into account both the strength of the supporting evidence and the expert comments from the voting round. The results of this revision were then arranged into one document by the first and last authors. During the summer of 2019, all WG members and all country representatives of the ESCP were invited to participate in a second online voting round on all the statements. Based on these surveys, all statements that reached an agreement of more than 90% were considered to be in agreement unless there were important reasoned objections by single voters. All other statements were revised and discussed at a meeting during the ESCP annual meeting in Vienna in September 2019. Following this meeting, all statements and the supporting text were edited by the first and last authors before the paper was sent for final revision and approval by all the authors combined with a third voting on revised statements.

WG I: Aetiology, follow-up including risk for cancer – statement of the problem and epidemiology

1.1 How is diverticular disease defined and how should it be classified?

The evolution of new diagnostic pathways and novel treatments has led to a diversity of terms such as asymptomatic and symptomatic diverticulosis, diverticular disease, acute and chronic diverticulitis and some other subgroup definitions. Unfortunately, this variety causes confusion. To establish clear definitions is important in the area of diverticula-related clinical and scientific communication.

Numerous classifications and modifications describe the various stages of diverticular disease (7, 9). The first widely used classification by Hinchey (10) was intended as an intra-operative stratification of perforated diverticulitis with abscess or peritonitis enabling surgeons to adjust the surgical approach. It was later modified to preoperative use, incorporating CT findings (11). The German guidelines suggest a new classification that is currently under validation. It was developed on the basis of Hinchey/Wasvary and Hansen and Stock, and adapted to current diagnostic and therapeutic aspects (5, 12). The ESCP guideline committee has decided neither to create yet another classification nor to quote one of the existing ones. All the existing classifications lack reliable validation and none of them is generally accepted. The guideline committee has therefore used definitions based on evidence as far as possible with some overlap with existing classifications. Figure 1 displays terms used in this guideline project.

Diverticulosis vs diverticular disease

Diverticulosis of the colon (existence of false diverticula – outpouchings of mucosa and serosa through openings in the muscular layer of the bowel) develops in the majority of individuals in western countries with increasing age and usually remains asymptomatic (13, 14). Diverticulosis *per se* should not therefore be considered a disease. The term diverticular disease implies that there are symptoms related to the diverticula.

Symptomatic uncomplicated diverticular disease (SUDD)

Whether diverticula can lead to symptoms in the absence of inflammation or bleeding is controversial (15-17). The term symptomatic uncomplicated diverticular disease (SUDD) is used in some countries for patients with diverticula who experience abdominal symptoms (e.g. abdominal pain and bloating) and changes in bowel habit (e.g. diarrhoea, constipation or alternating bowel habit) in the absence of inflammation (3, 18). However, the term has not found general acceptance and a uniform definition does not exist (15). A major difficulty is the differential diagnosis between irritable bowel syndrome (IBS) and SUDD as there is an overlap between the two (18). Epidemiological studies have shown that IBS-like symptoms may develop after a bout of acute diverticulitis (19). A comparative study between SUDD and IBS found significantly different pain characteristics (20) with abdominal pain lasting > 24 h occurring more frequently in SUDD, but a recent large cohort study including individuals in a colonoscopy screening programme found no association between diverticulosis and abdominal pain (15). Currently, there is little evidence on how to manage SUDD.

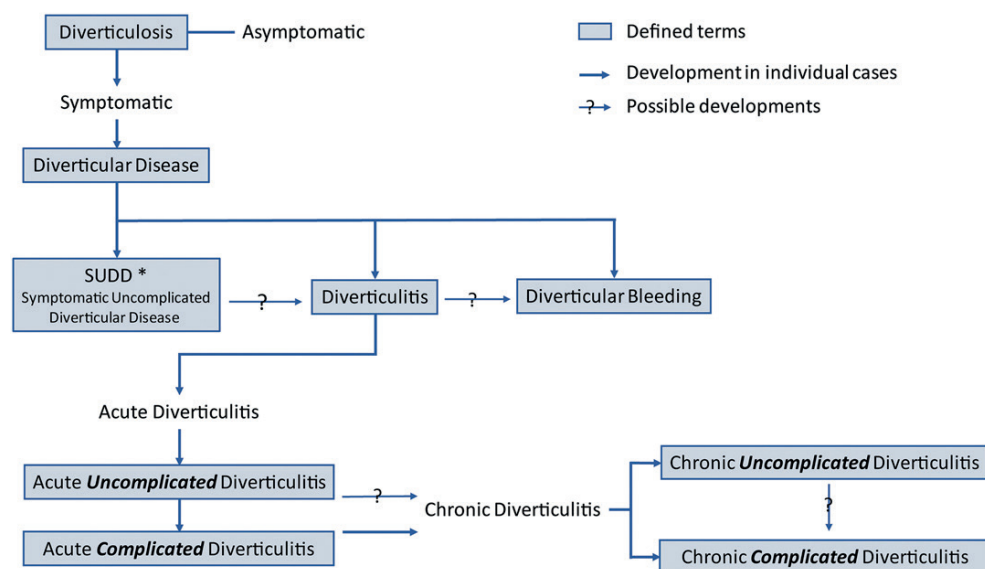


Figure 1 List of terms and stages used in the guideline. The flowchart shows the different stages of diverticulosis and diverticular disease. Note that although diverticulosis is a *conditio sine qua non* for the other stages, the different stages are not part of a continuous development and may appear independently in individual cases. *The term SUDD is controversial, as it remains unclear whether this is a disease of its own or whether it represents the coexistence of irritable bowel syndrome and diverticulosis.

Diverticulitis

The term diverticulitis describes a peridiverticular inflammation of the bowel wall and usually the surrounding tissue. The theory that the inflammation is a result of translocation of intestinal bacteria through the mucosa of the diverticulum on the basis of a weak barrier has lately been challenged (21) and the true aetiology is unclear.

Diverticulitis can be acute or chronic and complicated or uncomplicated with possible complications including abscess, perforation, fistulas, obstruction and bleeding (3). The severity of acute diverticulitis, mainly determined by cross-sectional imaging (CT scan, ultrasound) and laboratory tests (C-reactive protein), is decisive and guides management and treatment. In general, uncomplicated acute diverticulitis is differentiated from complicated acute diverticulitis. The cut-off is poorly defined but depends on the degree of inflammation.

Acute uncomplicated diverticulitis

Acute uncomplicated diverticulitis is inflammation in a diverticula-bearing bowel segment and the surrounding tissue without signs of perforation (extraluminal air) or abscess formation.

Acute complicated diverticulitis

Typical complications of acute diverticulitis occur if the inflammatory process extends beyond the colonic wall. However, peridiverticulitis alone is not considered complicated disease. A covered perforation with air bubbles in proximity to the bowel, intra-abdominal abscess adjacent to the inflamed segment (Hinchey Ib, according to Wasvary) or distant (Hinchey II) and free perforations with purulent or faecal peritonitis (Hinchey III and IV) represent the major manifestations of acute complicated diverticulitis (11).

Chronic diverticulitis

If an acute diverticulitis does not resolve completely, chronic diverticulitis can develop. Wall thickening or chronic mucosal inflammation in the absence of stenosis is called chronic uncomplicated diverticulitis. Complicated chronic diverticulitis includes both stenotic disease, which may lead to acute bowel obstruction, and fistulation most commonly to the urinary tract.

Diverticular bleeding

Diverticular bleeding is reported to account for about 35% of painless lower gastrointestinal bleeding and occurs in up to 50% of elderly patients with diverticulosis (5). The exact incidence is difficult to estimate, however. Frequently, the bleeding site cannot be identified, and coexisting diverticula may then falsely be reported as the bleeding cause.

Diverticular bleeding is arterial and occurs from rupture of the intramural branches of the marginal artery at the dome or neck of the diverticulum. Trauma from mechanical or chemical causes within the lumen of the diverticulum leads to injury to the penetrating vessels and bleeding. Histopathological examination of diverticular bleeding sites has shown absence of diverticulitis (22), but bleeding may occur during inflammation as

well. If surgery is required, precise localization of the bleeding site is crucial for any surgical procedure. Colonic resections in patients with diverticular bleeding and an unclear localization have shown a postoperative mortality of 43% in comparison to 7% in patients with defined bleeding localization (23). There are separate guidelines for the management of lower gastrointestinal bleeding which is therefore not part of this guideline.

The following statements are definitions by agreement of the guideline group.

Statements

1.1.1 Diverticulosis means an asymptomatic presence of diverticula and is per se not a disease.

Agreement 97% (second voting)

1.1.2 Diverticular disease is defined as diverticulosis with related symptoms or complications.

Agreement 100% (consensus meeting)

1.1.3 Clinical and scientific communication on diverticular disease must use accepted definitions.

Agreement 100% (second voting)

1.1.4 It is unclear whether SUDD – as defined by abdominal symptoms without proven inflammation or bleeding – can be considered a disease of its own or whether it represents the coexistence of IBS and diverticulosis.

Evidence level 4. Agreement 100% (consensus meeting)

1.1.5 Diverticulitis should be associated with symptoms and signs of peridiverticular inflammation proven by cross-sectional imaging and laboratory tests. Diagnosis should differentiate between uncomplicated and complicated as well as acute and chronic diverticulitis.

Evidence level 4. Agreement 97% (second voting)

1.1.6 Diverticular bleeding, very probably caused by a mechanical disruption of a vessel, occurs mostly painlessly without preceding diverticulitis. Patients with possible diverticular bleeding often need hospitalization with multidisciplinary treatment options and an urgent or semi-urgent endoscopic evaluation.

Evidence level 4. Agreement 93% (second voting)

1.2 What is the prevalence of diverticulosis?

By far the majority of individuals with diverticulosis remain asymptomatic throughout life (12). Therefore, the incidence of diverticulosis is difficult to estimate. Most data come from autopsy studies. A prospective study from Taiwan in asymptomatic subjects undergoing colonoscopy for a health screening revealed a frequency of colonic diverticulosis of 256 out of 1899 asymptomatic subjects (13.5%) ranging from 4.9%

in young adults (< 39 years) to 74.4% in the group > 70 years of age. There was a clear preponderance of men (24). In western countries with a predominant Caucasian population, the prevalence is higher (14, 15). Estimated rates of diverticulitis in patients with known diverticulosis are as low as 1%–4% or 1.5–6.0 per 1000 patient-years (25). Diverticulosis and associated clinical problems are most likely to occur in older age groups. However, although diverticula still are most frequent in elderly individuals, evidence is emerging that the condition has increased particularly in younger subjects under 45 years of age (26).

1.3 What is the incidence of uncomplicated and complicated diverticulitis and what are the annual healthcare costs for diverticulitis in Europe?

Although there is quite a variability of frequency rates for diverticulitis in the literature, there is some evidence that the incidence of diverticulitis has risen over the last years particularly in younger adults and women. There are almost no population-based data. Nearly all studies refer to the number of hospital admissions. A recent Italian study found an overall rate of 48 hospital admissions for acute diverticular disease per 100 000 inhabitants in 2015, and a yearly increase of over 3% from 2008. Interestingly, the age-specific rate was constant for older ages and there was only a slight increase for the younger age groups; thus some of the increase of the overall rate might be attributed to the aging population. The overall rate of hospital admissions for acute diverticular disease per 100 000 hospitalizations was 248 with an annual increase of 7.5% from 190 in 2008 to 310 in 2015 (27). From the USA, a prevalence of 92/100 000 persons with a preponderance of women has been reported (28). In the Netherlands, approximately 22 000 patients per year are referred to secondary care with diverticulitis. Ten per cent of these patients will develop complications such as abscess or perforation and will require further treatment in the form of close observation, antibiotics, percutaneous drainage or surgery (29). Due to uncertainties about the incidence, it is difficult to estimate the health economic burden of diverticulitis and there are no reliable calculations

1.4 What are the risk factors for diverticulosis, diverticulitis and its complications?

The formation of diverticula and the pathogenesis of diverticular disease is multifactorial and as yet not completely understood. Traditionally, the factors are thought to include older age, environment (diet, physical activity) and intestinal motility. Obesity is a major risk factor with a linear relationship and a relative risk for each 5-unit body mass index increase of 1.28 (95% CI 1.18–1.40) for diverticular disease, 1.31 (95% CI 1.09–1.56) for diverticulitis and 1.20 (95% CI 1.04–1.40) for complicated diverticular disease (defined as bleeding, abscess or perforation)(30). Recent research has identified other factors, such as genetic patterns, altered tissue composition and malfunction as associated with neuro-gastrointestinal disturbances (21). Colonic diverticula may occur in all segments of the colon but mostly in the sigmoid colon, with the second most common site in the right colon (31).

For practical reasons, risk factors for the development, appearance and outcome of acute diverticulitis are split into noncontrollable factors (age, sex and genetics) and factors that can be influenced.

Twin studies have demonstrated that a genetic component is present in the development of diverticulosis (32, 33). Few genetic studies have identified the actual genes that are susceptible culprits. Genetic connective tissue disorders like Ehlers–Danlos and Marfans syndrome have been linked to the development of diverticulosis in young age (34, 35). Some studies indicated that genes involved in immunity, extracellular matrix, cell adhesion, membrane transport and intestinal motility may be related to diverticular disease (36–38). However, the exact mechanisms remain to be shown.

Food and lifestyle are among the commonly discussed controllable risk factors, particularly dietary fibre. Epidemiological studies indicate that dietary fibre has a protective effect against development of diverticulosis and diverticulitis (39, 40). In addition, nuts, grains, corn and popcorn have been shown in big cohort studies to be protective against the development of diverticulitis (41). Red meat and smoking are possible risk factors (21).

Obesity is a risk factor for developing diverticulosis, diverticulitis and diverticular bleeding while physical activity is protective (42–45).

Commonly used drugs, such as nonsteroidal anti-inflammatory drugs, aspirin, acetaminophen, corticosteroids and opioids increase the risk of diverticular disease, particularly complicated diverticulitis (46).

In Denmark, 12%–17% of all hospitalizations for diverticulitis are for complicated diverticulitis with a marked increase of 43% in absolute numbers between 2000 and 2012 (47). Similar trends have been reported from Scotland (48).

Acute complicated diverticulitis comes with considerable mortality. In the largest series of Hinchey Ib–II diverticulitis ($n = 3148$, nationwide Danish registry), 8.7% of patients died within 30 days from admission, and 2.5% of those discharged alive died within 30 days from discharge; age and use of glucocorticoids were the main independent risk factors for death in multivariate analysis (49). Following an episode of acute diverticulitis with abscess formation, there is a marked risk for recurrence. The nationwide Danish registry data show recurrence rates of 9%–24%. Most recurrences and recurrence-related mortality occurred within the first year (50).

Mortality risk increases even more in the case of free perforations with peritonitis. A Dutch series from 1990 to 2005 found it to be as high as 26.5% during initial hospital stay with an overall 5-year survival of just 53%, mainly caused by the poor general health of the patients (51).

Both the risk of a subsequent free perforation and the risk of death decrease with the number of previous episodes (49, 52). The first episode of complicated diverticulitis is by far the most dangerous.

Statements

1.4.1 The development of diverticulosis is multifactorial and risk factors include age, genetic predisposition and obesity. The pathogenesis from diverticulosis to diverticulitis and its complications can be influenced by lifestyle and medications.

Evidence level 2. Agreement 100% (consensus meeting)

1.4.2 Acute complicated diverticulitis is associated with considerable short-term and long-term mortality. The risk of severe complications is highest at the first episode of diverticulitis and decreases with the number of recurrences.

Evidence level 2. Agreement 100% (second voting)

1.5 How should patients be followed-up after an episode of uncomplicated and complicated diverticulitis?

Due to the generally benign course of diverticulitis a routine follow-up of the disease itself seems only justified in unresolved complicated cases. However, although the widespread use of abdominal CT in the acute setting has made the diagnostics more accurate, the differentiation between diverticulitis and colorectal cancer (CRC) is still difficult in some cases. Most previous guidelines recommended routine colonoscopy some weeks after an episode of acute diverticulitis (6). The rationale was that early detection of CRC in misdiagnosed patients could reduce the chance of dissemination. No randomized trials to investigate the usefulness of this practice (by comparing cancer-specific survival with and without endoscopy) exist. Many primarily retrospective studies have investigated detection rates for CRC with colonoscopy after acute diverticulitis. However, meta-analyses of data have been troubled by the heterogeneity of the studies, the lack of a valid reference population, inconsistent reporting of CT verification of the diverticulitis episode, inconsistent definitions of uncomplicated and complicated diverticulitis and the lack of information about ongoing symptoms in the included patients (53-57).

Routine colonoscopy after an episode of conservatively treated complicated diverticulitis is generally accepted, as the prevalence of CRC is between 7.9% and 10.8% in this group (53, 55, 56).

For patients with CT verified uncomplicated diverticulitis, the two most recent meta-analyses have calculated a prevalence of CRC of 0.5% and 1.2% respectively due to the inclusion of different studies (55, 56). Furthermore, in the meta-analyses different reference populations are used leading to different conclusions. Meyer et al. calculated the prevalence of CRC after uncomplicated diverticulitis to be higher than that in the rest of the population whereas Rottier et al. found these prevalences to be similar. It should be noted that the prevalence of undiagnosed CRC in the asymptomatic background population can only be estimated. Detection rates of CRC in screening programmes vary between 0.1%(58) and 1%(59) (mostly around 0.5%(60)), depending on the age and risk profile of the included population. Screening probably overestimates the prevalence of CRC in asymptomatic patients, as participation rates are usually far below 50% and symptomatic and high-risk patients probably are more likely to attend. Also,

incidence rates for CRC have been used to estimate the prevalence of undiagnosed CRC in the population (55, 61), which has the weakness that it is uncertain how long the CRC existed before diagnosis.

After a CT verified uncomplicated diverticulitis, colonoscopy is usually part of the normal work-up of symptomatic patients (bleeding, changed bowel habits or ongoing pain). Controversy exists whether asymptomatic patients need endoscopic follow-up.

Statement

1.5.1 Endoscopic follow-up: for patients with symptom-free recovery after a single episode of CT verified uncomplicated diverticulitis endoscopic follow-up remains controversial and may not be necessary. All other patients treated without resection for acute diverticulitis should be followed up with an examination of the colon at least 6 weeks after the acute episode, if not done within the last 3 years.

Evidence level 3. Agreement 100% (third voting)

WG II: Imaging, indication and classifications – initial evaluation of diverticulitis and imaging

2.1 How can clinical findings be correlated to the severity of the disease?

Before the introduction of current imaging modalities, acute diverticulitis was a diagnostic challenge (62). A diagnosis of acute diverticulitis based solely on clinical findings is incorrect in more than 50% of cases (63). Together with other clinical findings, laboratory tests may be helpful to guide the clinician in the diagnosis (64). Several studies indicate that C-reactive protein levels are correlated to the severity of disease and recurrence rates; however, certain discrimination between the stages of the disease is not possible (65–68). Existing studies investigating the correlation between clinical findings and staging at imaging are very heterogeneous and generally not of high quality (29). Clinical findings may lead the clinician, however, when deciding the urgency of imaging and intervention.

Statement

2.1.1 There is a poor correlation between clinical findings and severity of the disease.

Evidence level 2. Consensus 100% (consensus meeting)

2.2 When should imaging be obtained on index and successive presentations of disease? (Which cases can be treated in primary care without imaging?)

Due to the low diagnostic accuracy of a clinical evaluation, imaging is generally required to confirm the clinical suspicion of acute diverticulitis in primary and secondary care, especially in patients with no previous diagnosis of diverticulitis (64, 69, 70). Even successive presentation of diverticulitis may require imaging to confirm the diagnosis.

However, as the course of acute uncomplicated diverticulitis even with small abscesses is benign (71), and severe complications are rare with low C-reactive protein levels, an observational strategy without imaging may be adequate in mild cases, especially in frequent recurrent disease (69). If no imaging is obtained, elective endoscopic examination, if not recently done, may be helpful for differential diagnosis.

Statement

2.2.1 Imaging is required to confirm the diagnosis of acute diverticulitis if there is no prior diagnostic information.

Evidence level 2, Strong recommendation. Consensus 100% (consensus meeting)

2.3 What is the most appropriate imaging tool to diagnose acute diverticulitis?

CT, ultrasound and MRI are possible imaging modalities that have been studied as tools to identify and classify diverticulitis. CT has a high sensitivity and specificity in the diagnosis of acute diverticulitis (72). Although abdominal ultrasound in expert hands has a high diagnostic accuracy, it has not gained widespread popularity (73). Ultrasound has the advantages of avoiding ionizing radiation and easy repetition if needed and it can be useful in pregnancy (72, 74). However, it is less accurate for abscess identification and exclusion of other gastrointestinal issues. A modified Hinchey classification cannot be assessed by ultrasound evaluation (75, 76). MRI is highly sensitive and specific in the differential diagnostics of diverticulitis (77). However, as it is time consuming and less available than CT it has not found wide acceptance. MRI is an alternative when ultrasound is inconclusive in pregnant women as well as after the acute phase to assist in differential diagnoses.

Statement

2.3.1 CT is recommended as the first-line investigation in suspected diverticulitis. Ultrasound and MRI are alternatives.

Evidence level 2, Strong recommendation. Consensus 100% (consensus meeting)

2.4 Which CT classification is appropriate?

There are many classifications in the literature but most of the published papers use either the Hinchey classification or a modified version of it. However, the Hinchey classification was originally a classification of intra-operative findings in patients with perforated diverticulitis and included only patients with abscesses or free perforations. One should be aware that the most frequently used modification by Wasvary also includes mild phlegmonous disease in the absence of complications (11, 78-83). It is useful for classifying both acute uncomplicated and complicated diverticulitis although there is little validation.

Statement

2.4.1 No CT classification is superior to others as a diagnostic tool for acute diverticulitis. Each centre should choose their preferred classification in communication with available radiologists.

Evidence level 5, Conditional recommendation. Consensus 100% (third voting)

WG III: Nonsurgical management of diverticulitis and dietary recommendations**3.1 Should uncomplicated diverticulitis be treated with antibiotics?**

Two randomized clinical trials (AVOD(84, 85) and DIABOLO(71, 86)) were performed comparing antibiotic and nonantibiotic treatment in immunocompetent and nonseptic patients with uncomplicated acute diverticulitis. No differences in time to recovery from the initial episode or in hospital stay were seen in the two trials. Furthermore, no differences were observed in the two trials regarding rates of complicated diverticulitis and the need for sigmoid resection after the initial diverticulitis episode and on long term (up to 11 years), in rates of recurrent diverticulitis, and in the need for sigmoid resection during the initial diverticulitis episode. Slightly but nonsignificantly more (elective) sigmoid resections were performed in the nonantibiotic group at 24 months (DIABOLO trial). This may have been caused by a lower threshold for surgery in the nonantibiotic group as they may have felt undertreated for their initial episode. Antibiotic-related morbidity occurred in 8.3% of patients in the antibiotic group from the DIABOLO trial. Two recent meta-analyses of the two randomized trials concluded that patients can be treated safely without antibiotics (87, 88). Cross-sectional imaging to confirm the diagnosis of uncomplicated diverticulitis was performed in both randomized trials and is encouraged in this guideline (Statement 2.2.1). However, if imaging in mild cases is not obtained, an observational strategy without antibiotic treatment seems justified as there is no evidence whatsoever for a positive effect of antibiotics in this situation.

Statement

3.1.1 Patients with acute uncomplicated diverticulitis do not require antibiotics routinely. Antibiotic treatment should be reserved for immunocompromised patients and patients with sepsis.

Evidence level 1, Strong recommendation. Consensus 100%, consensus meeting

3.2 What is the role of antibiotics in complicated diverticulitis?

Little evidence exists about antibiotic treatment in patients with complicated diverticulitis. Many patients with complicated diverticulitis are critically ill and it seems unethical to investigate the role of antibiotics in these patients. Patients who might be eligible for nonantibiotic treatment are those with small abscesses or small air bubbles around the sigmoid. In the above-mentioned AVOD study (84), patients with radiological signs of complications were excluded. The Dutch DIABOLO trial did include patients with small abscesses on CT (71). However, the number of patients in this category was very small and no final conclusions can be drawn. There are several

cohort studies investigating patients with pericolic air, showing that they have the same prognosis as patients with uncomplicated diverticulitis (89-91). However, in nearly all of these studies patients were treated with antibiotics (92).

Statement

3.2.1 Patients with radiological signs of complicated diverticulitis should normally be treated with antibiotics.

Evidence level 3, Conditional recommendation. Consensus 100%, consensus meeting

3.3 Which group of diverticulitis patients can safely be treated as outpatients?

Two recent systematic reviews (93, 94) have studied the evidence. One included 21 and the other 19 studies including one randomized trial (95) comparing inpatient and outpatient treatment for patients with uncomplicated diverticulitis, and comparable rates of readmission were found. The 19 studies combined showed a pooled readmission rate of 7%, very low rates of surgical or percutaneous interventions (0.2%) and potential healthcare cost savings up to 82%. Most studies only selected patients as outpatient treatment candidates based on patient characteristics (such as absence of comorbidities or immunosuppressed state), clinical condition (such as having uncomplicated diverticulitis and ability to tolerate oral intake) and patients' social environment (adequate family and social network). The second review published in 2019 included 21 studies and found a failure rate of 4.3% but highlighted that there were no criteria of failure, which makes patient selection difficult.

Statement

3.2.2 For patients with an adequate social network tolerating oral intake, outpatient treatment of uncomplicated diverticulitis seems to be safe in the absence of sepsis, significant comorbidity and immunosuppression.

Evidence level 2, Conditional recommendation. Consensus 97% , consensus meeting

3.4 Which supportive measures should be recommended in the acute stage of diverticulitis?

Although dietary restrictions and bed rest have been suggested as part of the treatment of acute diverticulitis, no benefit has ever been proven in studies. Many surgeons have traditionally recommended a low residue diet, but there is little evidence to support this practice. Two observational studies showed that an unrestricted diet is not associated with an increase in the rate of diverticular complications. A retrospective study showed no increase in complications in a group of patients with a solid food diet compared to several types of dietary restrictions (96). A prospective single-arm study with an unrestricted diet found an 8.1% complication rate after 6 months, which is comparable to rates in the literature on uncomplicated diverticulitis (97). Additionally, a randomized trial found no increased pain scores, no increased length of hospital stay and no treatment failures in patients with an unrestricted oral regimen compared to

an intravenous regimen including a minimum 24 h of fasting (98). Notably, this trial primarily compared oral and intravenous antibiotics which may have affected its results. Bed rest has not been studied at all. In addition, all patients with acute uncomplicated diverticulitis included in studies regarding outpatient management with or without antibiotics have had oral antibiotics with comparable outcomes as in the literature.

Statements

3.4.1 *There is no evidence to support dietary restrictions. An unrestricted diet (when tolerated) is preferable.*

Evidence level 3, Conditional recommendation. Consensus 93% (second voting)

3.4.2. *Any evidence regarding bed rest is lacking and, since imposed physical inactivity may impair the patients' general condition, bed rest is not recommended.*

Evidence level 4, Conditional recommendation. Consensus 100% (second voting)

3.5 *Are medical agents (mesalazine, rifaximin, probiotics) useful to prevent recurrences or persistent symptoms after an episode of acute diverticulitis?*

Several medical agents have been studied for their ability to prevent recurrent diverticulitis or persistent symptoms after an episode of acute diverticulitis: mesalazine (anti-inflammatory agent), rifaximin (nonsystemic, broad-spectrum nonabsorbable antibiotic) and probiotics. Mesalazine has been studied most thoroughly. A recent systematic review including seven randomized trials showed a pooled risk ratio for recurrent diverticulitis of 0.90 (95% CI 0.61–1.33) for mesalazine treatment compared to no treatment or placebo (99). Mesalazine may reduce global symptom scores. This has only been investigated by two trials including few patients (77 mesalazine and 76 control patients)(100, 101). The effect of 7–10 days per month rifaximin was assessed in one proof-of-concept randomized clinical trial (102) (rifaximin vs placebo) and two observational studies (103, 104) (rifaximin vs mesalazine). The randomized clinical trial found no difference in recurrent diverticulitis rates at 48 weeks in the intention-to-treat analysis, although some benefit of rifaximin was seen in additional analyses that were adjusted for several confounders. However, the number needed to treat is high and it is hence not clinically useful. The two observational studies comparing rifaximin and mesalazine found opposite results – one was in favour of rifaximin and the other in favour of mesalazine. Probiotics have been the topic of two randomized trials demonstrating conflicting results. One trial compared a combination of probiotics and mesalazine with mesalazine monotherapy (101). The probiotics/mesalazine group yielded the highest rate of recurrent diverticulitis and gastrointestinal complaints. The other trial found lower rates of recurrent diverticulitis in the probiotics group compared to the control (no treatment) group, but this trial included only 43 and 40 patients per group respectively and followed patients for only 3 months (105).

Statement

3.5.1. From the available medical agents, neither mesalazine, rifaximin nor probiotics can be recommended to prevent recurrent diverticulitis or persistent complaints after an episode of acute diverticulitis.

Evidence level 3, Conditional recommendation. Consensus 96% (second voting)

3.6 Should a high-fibre diet be recommended following an episode of acute diverticulitis?

A recent systematic review identified only two randomized studies assessing the effect of fibre modifications following an episode of acute diverticulitis (106). Both studies were conducted over 30 years ago and included only 20 and 56 patients, respectively. A three-arm randomized cross-over intervention study showed a higher proportion of patients being symptom free after 1 month of fibre supplements compared to a high-fibre diet. A retrospective cohort study demonstrated a lower recurrence rate in patients adhering to a high-fibre diet compared to patients not adhering to this diet (107). This is in line with large epidemiological cohort studies concluding that a high-fibre diet is associated with a lower risk of diverticular disease (39, 40, 108). Although this evidence suggests that a high-fibre diet may be beneficial in the prevention of diverticulitis and its recurrence or persistent symptoms, no final conclusions can be drawn due to the limitations of these studies.

Statement

3.6.1 Although a high-fibre diet may be recommendable for general health purposes, there is little evidence that it can prevent recurrent episodes or persistent symptoms in patients with acute diverticulitis.

Evidence level 3, Conditional recommendation. Consensus 93% (second voting)

3.7 What is the appropriate treatment strategy for patients with a diverticular abscess in the acute setting?

The management of acute diverticulitis with abscess formation consists of two different topics: how to manage these abscesses in the acute stage of disease and whether to perform an elective resection due to the complicated nature of this initial episode (see Statement 5.2.1). Diverticular abscesses can initially be treated with antibiotics and/or percutaneous drainage and/or surgery. A great number of studies have assessed the risk of treatment failure in one or more of these treatment strategies. However, no randomized data are available, and the observational studies suffer from high risk of selection bias. In almost all studies abscesses are larger and patients more severely ill in percutaneous drainage groups compared to the antibiotic groups, and in the surgical groups compared to nonsurgical groups, hampering the comparison of outcomes between these groups. A recent systematic review including 42 studies found comparable rates of treatment failure for antibiotics (19.9%), percutaneous abscess drainage (20.8%) and nonoperative management (20.6%)(109). Mortality rates increased with increasing invasiveness of treatment: 0.6% for antibiotics, 1.1% for nonoperative, 1.6% for percutaneous drainage and 12.1% for surgery. A recent large multicentre observational study including 447

patients demonstrates a significantly higher rate of treatment failure in the percutaneous drainage group compared to antibiotic treatment group (36% vs 24%, $P = 0.013$) and more complications in a subgroup of patients with a large or distant abscess (Hinchey II) when undergoing percutaneous drainage compared to antibiotics (12% vs 4%, $P = 0.032$), although these results were probably affected by selection bias as previously mentioned (110). In an attempt to eliminate this selection bias as much as possible in observational data, a multivariate analysis has been performed showing that percutaneous drainage was not independently associated with treatment failure (OR 1.47, 95% CI 0.81–2.68). In addition to earlier studies indicating 3 cm as the best cut-off above which treatment failure is more likely, multivariate analysis in this study showed an abscess cut-off size of 3 cm as the best predictor for treatment failure and 5 cm for the need for emergency surgery. However, in subgroups of patients with abscesses larger than 3 and 5 cm, respectively, percutaneous drainage was not able to decrease the rates of treatment failure. In summary, the risk of adverse outcomes increases with abscess size, but the role of percutaneous drainage remains unclear.

Statement

3.7.1 Although the role of percutaneous drainage of abscesses in acute diverticulitis is not completely clear, it may be considered in patients with an abscess larger than 3 cm. Emergency surgery should be kept as last resort for patients failing other nonsurgical treatments.

Evidence level 3, Conditional recommendation. Consensus 100% (consensus meeting)

WG IV: Emergency surgery for acute diverticulitis

4.1 What are the indications for abdominal exploration in patients with acute diverticulitis?

Clinical evaluation alone is very subjective and has not been assessed in many studies. Traditionally, clinical signs of sepsis in combination with generalized peritonitis were considered an indication for surgery. This practice is based on experience rather than evidence. Radiologically detected extraluminal air has usually been considered as a sign of perforation with indication for surgery. There is little evidence, however, whether pericolic or free air alone is an indication for exploration or not. If extraluminal air is used as a surrogate marker for abdominal exploration, there are five retrospective and three prospective cohort studies with a total of 1470 patients (89-91, 111-115). Most of the studies are of poor quality with a low number of patients. Between 0% and 10% of all patients required a surgical procedure.

Free fluid has been suggested to be another surrogate marker, but it is frequently found in uncomplicated diverticulitis as well, rendering the use as a surrogate marker for complicated disease difficult (84).

Statement

4.1.1 It seems fairly safe to observe immunocompetent haemodynamically stable patients even if there are radiological signs of extraluminal air. Immediate surgery should be considered in haemodynamically unstable or septic patients.
Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

4.2 Which surgical approach is appropriate in patients with faecal peritonitis (overt perforation)?

There are no randomized trials that involve nonsurgical or nonresectional treatment for faecal peritonitis (116-119). Some patient series have investigated laparoscopic closure of a perforation combined with laparoscopic lavage but there is little evidence to support this practice (120). There are some studies suggesting damage control with a second look within a couple of days (116, 121). Neither are established techniques. There are no randomized trials comparing the laparoscopic vs the open technique for faecal peritonitis and existing nonrandomized trials are heavily influenced by selection bias.

Statement

4.2.1 The surgical approach in patients with faecal peritonitis should be related to the experience of the surgeon; there is no evidence supporting laparoscopic or open surgery. Resection is the treatment of choice.
Evidence level 4, Strong recommendation. Consensus 97% (second voting)

4.3 Which surgical approach is appropriate in patients with purulent peritonitis?

There are three recently published randomized trials comparing laparoscopic lavage to open surgery with sigmoid resection with or without primary anastomosis. In the three studies, a total of 358 Hinchey III patients were included of whom 185 underwent laparoscopic lavage (122-124). Several meta-analyses have been performed with somewhat different results (125-133). There are several noncomparative cohorts showing that laparoscopic lavage is feasible in selected patients (134).

Laparoscopic lavage reduces the risk for colostomy at 1- and 2-year follow-up but may in the short term result in intra-abdominal abscesses and overlooked free perforations or tumour perforations requiring reintervention (drainage or reoperation)(135, 136). Laparoscopic lavage is cheaper than resection and colostomy (Hartmann's procedure) (137-139).

Statement

4.3.1 Laparoscopic lavage is feasible in selected patients with Hinchey III peritonitis. Alternatively, resection is recommended.
Evidence level 2, Conditional recommendation. Consensus 93% (second voting)

4.4 What is the role of restoration of intestinal continuity with or without proximal faecal diversion in the management of acute diverticulitis?

Several studies have addressed the intestinal continuity during surgical treatment for acute diverticulitis. There are three cohort studies and four randomized trials (116-119, 140-142). The randomized clinical trials all include a diverting loop ileostomy in the primary anastomosis arm. None of the randomized clinical trials found a difference in morbidity or mortality between primary anastomosis and sigmoid resection with colostomy. Primary anastomosis will result in a lower stoma rate but may also increase the risk for complications. Many studies have used a diverting loop ileostomy. The DIVA arm of the LADIES trial has indicated that primary anastomosis is a safe option for Hinchey III and Hinchey IV patients compared to resection and a stoma (142). The larger cohort studies included both Hinchey III and Hinchey IV and one of the cohort studies included 67 721 patients (141). This study found a higher risk for complications in patients with anastomosis and diversion compared to colostomy.

Statement

4.4.1 Primary anastomosis with or without diverting ileostomy can be performed in haemodynamically stable and immunocompetent patients with Hinchey III or IV diverticulitis.

Evidence level 2, Conditional recommendation. Consensus 97% (second voting)

WG V: Elective surgery for diverticulitis

5.1 When should elective sigmoid colectomy be considered after recovery from uncomplicated acute diverticulitis?

Previously elective colon resection after the second episode of uncomplicated diverticulitis in order to prevent severe attacks was widely recommended (79, 143, 144). While sigmoid resection is effective to reduce the risk of recurrent attacks of diverticulitis, several cohort studies have shown that complications are most likely to occur at the first episode and prophylactic surgery to prevent complications is not indicated (52, 145). The only justifiable reason to operate on patients with recurrent disease or with ongoing symptoms after uncomplicated diverticulitis is to improve their quality of life (QoL). There are numerous retrospective cohort studies on elective surgery (146-151), some of them addressing QoL (150, 151). These studies are very heterogeneous and of low quality, with a high probability of selection bias and inconsistent findings (152).

Recently the short- and long-term results of the DIRECT trial have been published. This is the only randomized trial comparing elective surgery vs conservative management of patients with frequently recurrent diverticulitis or ongoing symptoms after an episode of diverticulitis (153, 154). The QoL after 6 month and after 5 years was significantly better for patients in the surgical group. However, the trial had several limitations. It was prematurely aborted, had a relatively small sample size and the observed difference in QoL between the groups was quite small. Furthermore, the inclusion criteria were very strict, only patients with frequent recurrences (more than two within 2 years) or

patients with ongoing symptoms and radiologically or endoscopically proven ongoing inflammation were eligible. The complication rate in the operative group was high (15% anastomotic leakages).

Statements

5.1.1 Elective surgery to prevent complicated disease is not justified, irrespective of the number of previous attacks.

Evidence level 2, Strong recommendation, Consensus: 97% (second voting)

5.1.2 There is no evidence to support resection in symptomatic patients without radiological or endoscopic signs of ongoing inflammation, stenosis or fistula.

Evidence level 3, Strong recommendation. Consensus 97% (second voting)

5.1.3 The goal of elective surgery after one or more episodes of diverticulitis is to improve QoL. The indication should be individualized and based on the frequency of recurrences, duration and severity of symptoms after the attacks and the comorbidity of the patient.

Evidence level 3, Strong recommendation. Consensus 97% (second voting)

5.2 Should elective colectomy typically be offered/considered after recovery from a conservatively managed episode of acute complicated diverticulitis?

Traditionally most patients with acute complicated diverticulitis were treated with emergency surgery, which before the era of cross-sectional imaging was the only way to diagnose complicated disease with certainty (10). The introduction of CT and transcutaneous treatment of abscesses has revolutionized the treatment of abscesses and acute surgery is rarely required in these patients. It is quite likely that the frequent use of CT has also led to a stage migration, as the detection of small amounts of extraluminal air and small abscesses is much easier with up to date multidetector CT scanning. Many patients with covered perforations or even with distant free air are now initially treated conservatively with antibiotics alone. Several previous guidelines recommend elective resection after a complicated attack but there is little evidence to support this practice. Some retrospective cohort studies have reported higher recurrence rates after acute complicated diverticulitis (up to > 60%) compared to acute uncomplicated diverticulitis (15%–23%) whereas others report similar recurrence rates in both groups (84, 86, 155–157). A systematic review shows a recurrence rate of 25.5% in 7653 patients with diverticular abscesses (109). Other studies that are published later show mostly comparable rates of 25%–30% but ranging from 9% to 61% (50, 110, 158–162). Several studies included in the systematic review do not show an increased risk for complications in recurrent episodes; others (160) report a 63% complicated recurrence rate and the previously discussed large observational study (110) shows 43% of recurrences being complicated. It should be noted that a substantial number of patients can be treated nonoperatively again and the risk of recurrence requiring acute operation following conservative management of acute complicated diverticulitis is relatively low (159, 160). There is only one small trial which randomized patients with extraluminal air and/or abscesses to either elective surgery ($n = 26$) or observation ($n = 81$). The

majority of patients in the observation group did not require elective surgery. However, QoL was not evaluated in this trial (163).

Statement

5.2.1 The decision to operate on patients after a conservatively managed episode of acute complicated diverticulitis should follow the same principles as for patients with uncomplicated diverticulitis, resection is not recommended routinely.

Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

5.3 How should surgery of persisting abscesses and fistulas be performed and is there a role for nonsurgical treatment?

There are few high-quality studies investigating the management of persistent abscesses and fistulas due to diverticulitis. Some descriptive case series, focusing either on the open or the laparoscopic approach, supported resection with primary anastomosis when possible and contextual bladder resection if needed (164-172). Only one small retrospective cohort study investigated laparoscopic vs open surgery, demonstrating similar results (173). Although limited by the poor quality of included studies, two meta-analyses by the same first author reported no clear advantage of the laparoscopic approach (174, 175). Furthermore, the authors highlighted that the laparoscopic approach may be challenging and consequently should be performed by experienced laparoscopic surgeons. There is only scarce evidence for the use of a robotic approach (176, 177). The conservative management of fistulas is documented only in two older retrospective studies (178, 179). Although limited by several sources of bias, the results of these studies were in favour of surgical management when the patient's general condition allows it, as the conservative treatment is related to a high mortality rate and poor QoL. There is no evidence concerning oncological vs nononcological resection.

Statement

5.3.1 Fistulas or persistent abscesses should normally be treated with laparoscopic or open resection of the diseased bowel with or without anastomosis.

Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

5.4 Which surgical approach is most appropriate in elective surgery for diverticulitis (open/laparoscopic)?

Laparoscopic sigmoid resection for the treatment of diverticular disease is feasible in an elective setting (180-185). Three randomized controlled trials comparing laparoscopic to open sigmoid resection have been published (186-188). However, they were all underpowered, included different stages of the disease and reported inconsistent results. Only two of these conclude with better short-term outcomes with laparoscopic resection (187, 188) and none of the three demonstrated convincing superiority of the laparoscopic over an open approach in long-term results. Three meta-analyses about the role of mini-invasive surgery for elective surgery for diverticulitis have been published (189-191), two of which included nonrandomized studies (189, 190). The Cochrane review by Abraha et al. (191) analysed only the three existing randomized clinical trials.

They find it uncertain whether laparoscopic sigmoid resection has any substantial advantage over open sigmoid resection in diverticular disease. However, laparoscopic surgery has evolved since these trials were conducted and it is likely that laparoscopic resection has the same short-term advantages in diverticular disease as demonstrated for other diagnoses.

Statement

5.4.1 Elective colon resection for diverticulitis should preferably be performed laparoscopically when feasible.

Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

5.5 Should immunocompromised and young patients be treated differently?

In immunosuppressed patients, complicated diverticulitis appears to be more aggressive, with more frequent free peritoneal perforation and worse outcomes (192, 193). The incidence of complicated diverticulitis in patients after organ transplant is approximately 1% higher than in immunocompetent patients (194). Nonoperative management of renal transplant patients with uncomplicated diverticulitis is safe, with outcomes similar to immunocompetent patients. However, the optimal management of renal transplant patients with complicated diverticulitis remains unclear as both treatment choices and complication rates differed from immunocompetent patients (195). Comparison of elective colectomy in transplant patients after one episode vs multiple attacks of diverticulitis showed no differences in complication rates and mortality. Colectomy after a single attack of diverticulitis in transplant patients is not justified as the operative risk is higher in these patients (196).

Among immunocompromised patients, chronic corticosteroid users have the highest risk of emergency surgery and of recurrence, especially in the first year after a diverticulitis attack. There should be a low threshold for abdominal CT in their follow-up, to search for persistent fluid collections or pericolic inflammation, in which case elective surgery may be indicated (197).

In young patients elective surgery after one episode of acute diverticulitis has been suggested due to the supposedly higher risk of recurrences and a more aggressive presentation (198). In a systematic review including 4751 patients younger and 18 328 older than 50 years of age, patients younger than 50 years substantially differ from patients older than 50 years only in the risk for recurrent disease. Although the relative risk for requiring urgent surgery for recurrent disease may be higher in younger patients, the absolute risk difference was relatively small (7.3% vs 4.9%)(199). Nevertheless, controversy persists about whether younger patients have more aggressive attacks, and the effect of the disease on their QoL. However, recommendation of more liberal resection in younger patients is not supported by the evidence (200).

Statement

5.5.1 The decision for elective resection after an acute episode of diverticulitis in immunocompromised and younger patients should follow the same principles as in other patients and is not recommended routinely.

Evidence level 3, Conditional recommendation. Consensus 100% (consensus meeting)

WG VI: Technical considerations – special considerations**6.1 What is the role of leak tests in surgery for diverticular disease?**

The literature search did not show studies assessing intra-operative leak tests during surgery for diverticulitis. However, a systematic review and meta-analysis of 20 studies assessing intra-operative air leak test (ALT) during colorectal surgery concluded that evidence suggests that ALT is necessary to identify patients with a higher risk of colorectal anastomotic leakage (201). In addition, another systematic review assessed ALT and recommended intra-operative ALT, since it is relatively simple, inexpensive and allows for intra-operative revision of the anastomosis (202). This is further supported by the results of the largest randomized trial so far, comparing ALT to no ALT in 145 colorectal surgery patients, that demonstrated that ALT significantly reduces the incidence of postoperative clinical and radiological leaks (203). We suggest that, in the case of a doubtful air leak, the test should be repeated. Moreover, after a positive ALT, a test with methylene blue might be used to examine the extent and location of the leak.

Statement

6.1.1. An ALT of the colorectal anastomosis during surgery for sigmoid diverticulitis is recommended.

Evidence level 2, Conditional recommendation. Consensus 93% (second voting)

6.2 Which extent of resection is appropriate in an emergency setting?

Most literature regarding the extent of resection is based on retrospective data of elective surgery for diverticular disease (204-209). A recent case-control study did not show histological inflammation or diverticula at the resection margins to be correlated with the occurrence of anastomotic stenosis (206). Extending margins in the case of extensive diverticulosis seems unnecessary to prevent recurrent diverticulitis (209). However, with regard to the construction of an anastomosis, it seems important to resect the grossly inflamed bowel segment both proximally and distally. Limited data are available on the proximal resection margin, whereas more data are available on the distal margin. Evidence from studies comparing colo-sigmoid and colorectal anastomoses suggests that the latter has a lower frequency of recurrent disease (204).

Statements

6.2.1 In the emergency setting, the focus is to control sepsis and resect the perforated segment.

Evidence level 4, Conditional recommendation. Consensus 100% (consensus meeting)

6.2.2 In the case of resection and primary anastomosis, sigmoid resection down to the rectum with colorectal anastomosis should be done, with the proximal margin in as healthy colon as possible.

Evidence level 3, Strong recommendation. Consensus 100% (consensus meeting)

6.3 What is the preferred vascular approach in surgery for diverticular disease?

A meta-analysis, published in 2012, indicates no significant difference in anastomotic leak rate between preservation or ligation of the inferior mesenteric artery (IMA)(210). Results from a randomized, controlled trial comparing IMA preservation and ligation in patients undergoing surgery for diverticulitis (note that Hinchey III/IV were not included) show an improvement in intestinal function through a reduction in neo-sigmoid denervation (211). Results from a comparable randomized trial show clinical and radiological leakage rates to be lower in the IMA preservation group (212). More recent evidence, from both retrospective and prospective cohort studies, was either in favour of IMA preservation or inconclusive on its effect compared to IMA ligation (213-217). A recent review and meta-analysis failed to demonstrate a statistically significant difference in the anastomotic leakage rate comparing IMA preservation with IMA ligation (218). The authors conclude that, to date, there is insufficient evidence to recommend the IMA-preserving technique as mandatory in resection for left-sided colonic diverticular disease and the decision remains at the discretion of the operating surgeon. High ligation seems warranted in cases with diagnostic uncertainty or when cancer cannot be excluded (inconclusive CT, MRI or endoscopy), whereas IMA preservation might be beneficial in cases where the diagnosis is clear.

Statement

6.3.1 In cases where there is no suspicion of cancer, IMA-preserving surgery can be performed to optimize preservation of the vascularization and the autonomic nerves.

Evidence level 2, Strong recommendation. Consensus 97% (second voting)

6.4 What is the role of ureteral stents in elective resection for diverticular disease?

No results from prospective, randomized trials were available (219-221). Results from large population-based studies performed in the USA have shown that, after adjustment for other patient and clinical factors, ureteral stenting in surgery for diverticular disease is significantly associated with a longer operative time, as well as a longer length of stay and higher costs (219, 220, 222). Despite this, the benefits of ureteral stent use remain unclear, since the available literature indicates that selective stent use might have

led to confounding by indication. Evidence identifying patient populations that most probably benefit from ureteral stenting is not available yet.

Statement

6.4.1 Ureteral stenting is not recommended as a routine, due to increased costs and operative time, but may be appropriate in selected cases with severe complicated disease.

Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

6.5 Should the splenic flexure routinely be mobilized?

One retrospective study was identified that compared routine splenic flexure mobilization with no splenic flexure mobilization in elective surgery for diverticular disease (223). Data were derived from a population-based cohort, with innate risk of selection bias, and showed splenic flexure mobilization to be safe and feasible. Despite a trend towards an increased minor morbidity rate (defined as superficial or deep surgical site infection, pneumonia, unplanned intubation, urinary tract infection or deep vein thrombosis) after splenic flexure mobilization, no difference was found in major adverse events. One other retrospective study showed from univariate analysis that splenic flexure mobilization did not seem to contribute to the complication rate (224). From the literature, it is suggested that splenic flexure mobilization is performed on an individual basis, depending on the anatomy, disease extent, and the potential for the creation of a tension-free anastomosis (223).

Statement

6.5.1 Partial or full mobilization of the splenic flexure might facilitate the anastomosis being made of soft and compliant descending colon, by being brought down to the pelvic brim and anastomosed with the rectum without tension. It is up to the judgement of the surgeon whether this is necessary.

Evidence level 3, Conditional recommendation. Consensus 100% (second voting)

Acknowledgements

We thank all the national representatives who responded in the second voting round for their valuable contribution: Ondrej Ryska (Czech Republic), Georgios Pechlivanides (Greece), Jürgen Mulsow (Ireland), Jeroen W A Leijtens (Netherlands), Nuno Rama (Portugal), Victor Tomulescu (Romania), Gregor Norčič (Slovenia), Marcel Sadeghi (Sweden), Ugur Sungurtekin (Turkey), Ivan Dimitrijevic (Serbia). Further, we thank the ESCP guideline committee for initiating and supporting the project. Special thanks to Stefan van Dijk and the Dutch guideline group for providing their latest evidence tables.

Funding

The European Society of Coloproctology (ESCP) funded two face to face meetings in conjunction with the ESCP annual meeting. Otherwise, the project did not receive any funding.

Conflicts of interest

WK had fees for teaching and advice from the Institute Allergo San, Austria, and Falk, Germany; otherwise none of the authors reported a conflict of interest.

Ethical approval and informed consent

Ethic approval, patient consent, permissions to reproduce and clinical trial registration not relevant.

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The first part of the paper discusses the importance of understanding the local context in which a project is implemented. This includes a thorough analysis of the social, economic, and cultural factors that may influence the success or failure of the intervention. It is essential to engage with local stakeholders from the outset to ensure that the project is relevant and sustainable.

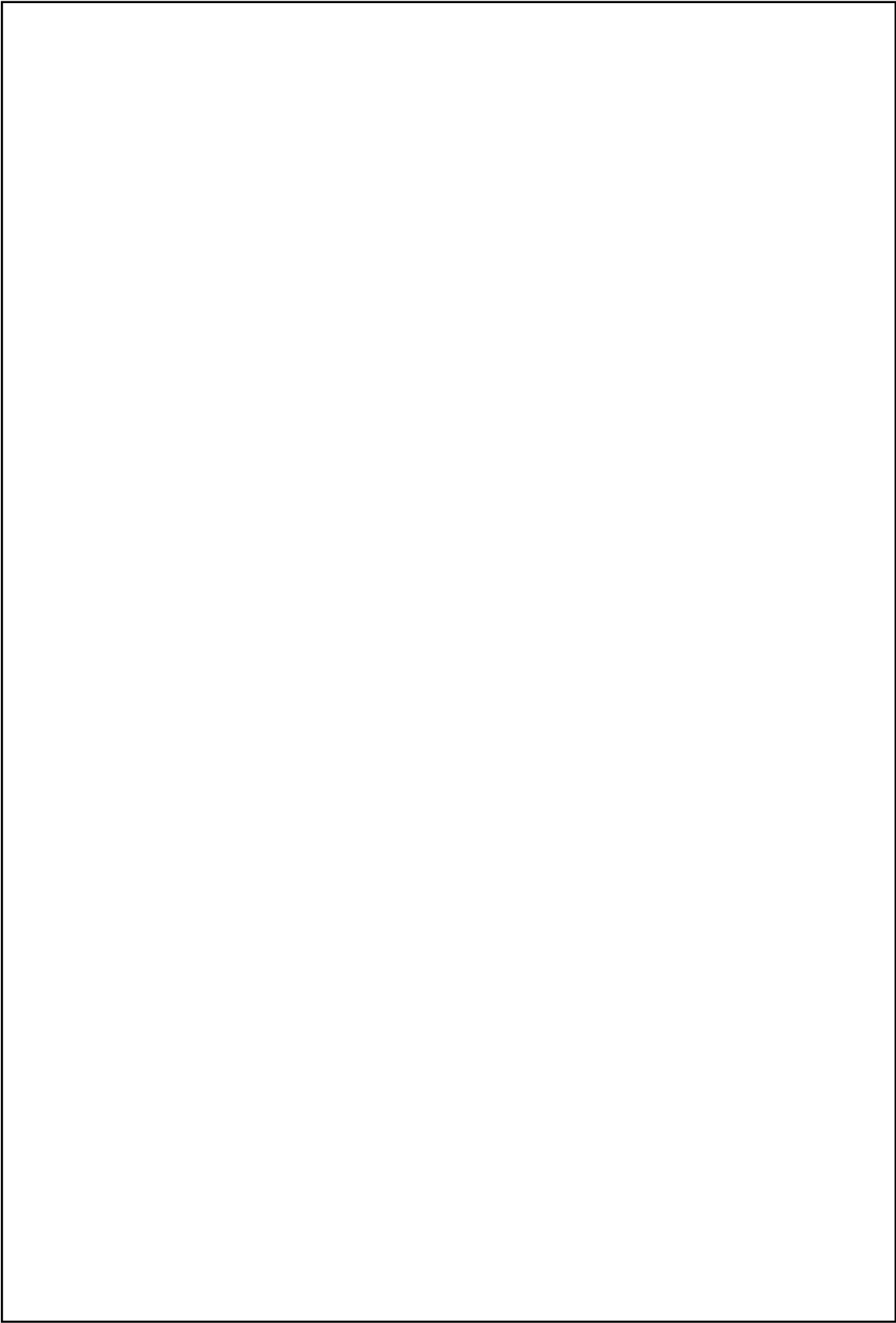
The second part of the paper explores the challenges faced by project managers in the field. These challenges often arise from limited resources, lack of infrastructure, and resistance to change. Effective communication and leadership skills are crucial to overcome these obstacles and ensure that the project remains on track.

The third part of the paper presents a case study of a successful community-based project. This example illustrates how a combination of local knowledge, external support, and a clear vision can lead to positive outcomes. The project focused on improving access to clean water and sanitation, which had a significant impact on the health and well-being of the community.

The final part of the paper offers conclusions and recommendations for future projects. It emphasizes the need for ongoing evaluation and adaptation, as well as the importance of building local capacity to ensure long-term sustainability. By following these guidelines, project managers can increase the likelihood of achieving their goals and making a lasting difference in the lives of the people they serve.

Part IV

Stoma-related complications



Chapter 10

Non-operative treatment as a strategy for patients with parastomal hernia: a multicentre, retrospective cohort study

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Colorectal Disease 20.6 (2018): 545-551

Abstract

Aim

Parastomal hernia is the most common complication following stoma construction. Surgical treatment is usually chosen over non-operative treatment, but a clear rationale for the choice of management is often lacking. This study aims to investigate reasons for non-operative treatment, cross-over rates and postoperative complications.

Method

A multicentre, retrospective cohort study was conducted. Patients diagnosed with a parastomal hernia between January 2007 and December 2012. Data on baseline characteristics, primary surgery and hernias were collected. For non-operative treatment patients, reasons for this treatment and cross-over rates were evaluated. For all patients undergoing surgery (surgical treatment and cross-overs), complication and recurrence rates were analyzed.

Results

Of the 80 patients included, 42 (53%) were in the surgical treatment group and 38 (48%) in the non-operative treatment group. Median follow-up was 46 months (interquartile range 24-72). The reasons for non-operative treatment were absence of symptoms in 12 patients (32%), comorbidities in nine (24%) and patient preference in three (7.9%). In 14 patients (37%) reasons were not documented. Eight patients (21%) crossed over from non-operative treatment to surgical treatment, of whom one needed emergency surgery. In 23 patients (55%), parastomal hernia recurred after original surgical treatment, of whom 21 (91%) underwent additional repair.

Conclusion

Parastomal hernia repair is associated with high recurrence and additional repair rates. Non-operative treatment has a relatively low cross-over and emergency surgery rate. Given these data, non-operative treatment might be a better choice for patients without complaints or with comorbidities.

What does this paper add to the literature?

Parastomal hernia is the most common complication after stoma construction. To date, no data exist on non-operative treatment as a treatment option. This paper analyses non-operative treatment and compares it with surgical treatment. By doing so, it provides a first step towards patient-centered treatment of parastomal hernia.

Introduction

Parastomal hernia is the most common complication following stoma construction, especially after end colostomy(1, 2). Incidence numbers depend on the type of stoma, with ileostomy leading to 0-6.0% herniation and colostomy to 3.0-39% herniation(2-4). Over 120,000 colostomies are created each year in the USA alone(5), potentially resulting in 3,600-46,800 parastomal hernias.

Preventative strategies such as prophylactic mesh placement or extraperitoneal colostomy have lowered these numbers, but they remain high(6-8).

Parastomal hernia commonly occurs within the first year after stoma formation, but the incidence increases over time(1). Parastomal hernias can be asymptomatic. However, when parastomal hernias become symptomatic, complaints can be discomfort, pain, bowel obstruction, problems with stoma appliance handling, leakage and incarceration(3). The majority of patients with parastomal hernia are managed primarily by hospital stoma care nurses (SCN), who therefore play an important role in the provision of care for patients with parastomal hernia(9). However, surgery remains the most common treatment of parastomal hernias. Surgical treatment can be performed both open and laparoscopically and with or without mesh augmentation, but there is no consensus. Recent research has focused mainly on surgical repair with mesh augmentation(10). However, mesh repair still results in recurrence rates of 6.9-17%(11).

Apart from surgery, non-operative treatment (NT) potentially is an appropriate alternative. The obvious benefit of this strategy is the absence of the risk of complications following surgical repair. On the other hand, the potential risk is emergency surgery for incarceration or strangulation, which is associated with higher complication rates than elective surgery(12, 13).

For inguinal hernia treatment, the NT strategy is generally accepted after being proven to be safe and cost effective(14-16). More recently, Verhelst *et al.* (17) found that non-operative treatment in patients with incisional hernia leads to a one-third cross-over rate with high rates of postoperative complications. However, whether this strategy could be useful for parastomal hernia has not yet been properly investigated. Only one study from 1984 describes the possibility of non-operative treatment(18). The study by Cevese *et al.*(18) was characterized by a number of methodological flaws: only 27% of all patients having a colostomy were examined, a variety of different surgical approaches for colostomy were included, and there was no definition of outcome. For these reasons, no robust conclusions could be drawn.

Therefore, the aim of this retrospective study was to identify the rationale for choosing NT or surgical treatment (ST) for parastomal hernia and to compare outcomes of both strategies in terms of complications, hernia recurrences and cross-over rates.

Method

A multicentre, retrospective study was performed. The study was approved by all participating hospitals' Institutional Review Boards. Informed consent was waived for participation in this study, because it was a retrospective records review. STROBE (Strengthening the Reporting of Observational studies in Epidemiology) recommendations for the reporting of observational studies were used(19).

All patients diagnosed with a parastomal hernia between January 2007 and December 2012 were included from the databases of the Erasmus University Medical Center Rotterdam, Academic Medical Center Amsterdam, Havenziekenhuis Rotterdam, and IJsselland Hospital Capelle aan den IJssel. Colostomies (end and loop), ileostomies (end and loop), and ileal conduits were included. The diagnosis of parastomal hernia could be made by the stoma care nurse or the surgeon and could be made clinically or radiologically. In all participating hospitals, experienced hernia surgeons were involved and both ST and NT were treatment strategies used for parastomal hernia. Since no international guidelines exist on this topic, the decision to choose either treatment was made in agreement between surgeons and patients. Patients were divided into two groups based on initial treatment strategy chosen directly after diagnosis: ST and NT. Only patients who were diagnosed with parastomal hernia in an elective setting were included. Patients with first presentation of parastomal hernia in an emergency situation were excluded, since NT is seldom a therapeutic option in these patients. Patient records and the electronic hospital database systems were reviewed. Patients were identified searching for DBC codes ('Diagnose Behandel Combinatie'; Diagnosis Related Groups) and ICD-9 codes (International Statistical Classification of Diseases and Related Health Problems). To minimize the risk of missing eligible patients, all codes regarding any abdominal wall hernia were searched for in the medical records of patients with a stoma.

Data collection

General patient characteristics, comorbidities, medical history, American Society of Anesthesiologists (ASA) grade, and information regarding primary surgery were recorded. Symptoms at first presentation were categorized into groups: pain, appliance leakages, aesthetic complaints, and bowel obstruction. Parastomal hernia size (defect of the abdominal wall fascia, as measured with ultrasound or axial CT imaging) and the presence of a concomitant incisional hernia were noted for European Hernia Society (EHS) classification (class I, size <5cm without a concomitant incisional hernia; class II, size <5cm with a concomitant incisional hernia; class III, size >5cm without a concomitant incisional hernia; and class IV, size >5cm with a concomitant incisional hernia)(20).

For patients in the ST group and cross-over patients from the NT group, reasons for ST and type of repair were noted and postoperative complications (infection, postoperative ileus, perforation, obstruction) were scored. In general, patients visited stoma nurses or surgeons on a regular basis. Data on recurrence and, if needed, additional surgical repair were collected. For patients in NT group, the reason of NT (absence of symptoms, comorbidity, obesity, patient preference) was noted.

Statistical analysis

Statistical analyses were performed with the SPSS Software Package (IBM SPSS Statistics for Windows, Version 21.0. Armonk, New York, USA). To test normal distribution of continuous variables, Levene's test for equality of variances was used. Continuous variables are presented as medians with interquartile ranges or as means with standard deviations, depending on the normality of data distribution. Categorical variables are presented as numbers with percentages (%). Differences between groups were compared using Mann-Whitney U test (continuous data) or chi-squared test (categorical data). In case of small groups ($n < 5$), Fisher's exact test was used. P values < 0.05 were considered statistically significant.

Results

A total of 80 patients were included from the hospital databases. Of these 80 patients, 42 patients (53%) were scheduled for ST. NT was chosen in 38 patients (48%). Reasons for NT were absence of symptoms in 12 patients (32%), comorbidities in nine (24%) and patient preference in three (7.9%). In 14 patients (37%) reasons were not documented. Eight patients (21%) of the 38 NT patients crossed over to ST. Of these eight patients, one patient had to undergo emergency surgery (2.63% of the total NT group). Median follow-up duration of all patients was 46 months (interquartile range was 24-72) and did not differ between the ST and NT group [respectively, 43.5 months (20.3-72.0) and 47.1 (28.5-96.2), $P = 0.823$].

Patient characteristics

Baseline characteristics of both groups are given in Table 1. Mean age in the ST group was 51 ± 15 years and 63 ± 12 in the NT group ($P < 0.001$). There were less patients with COPD in the ST group than in the NT group ($n=0$ (0%) *vs* $n=4$ (11%), $P = 0.047$). Ten patients (24%) in the ST group were operated for a malignancy compared to 23 patients (62%) in the NT group ($P < 0.001$). Consequently, more patients in the ST were operated for other reasons ($n=16$ (39%) *vs* $n=5$ (14%), $P = 0.020$). All other characteristics (baseline characteristics, stoma types, and complications after primary surgery) were not statistically significantly different between the ST and NT groups.

Parastomal hernia characteristics

Parastomal hernia characteristics are listed in Table 2. The mean hernia size was 3.59 ± 1.96 cm in the ST group and 3.43 ± 1.37 cm in the NT group ($P = 0.762$). Size details were not available for 18 patients (43%) of the ST group and 18 patients (47%) of the NT group because of the absence of ultrasound or CT images. There were fewer asymptomatic patients in the ST group compared with the NT group ($n=1$ (2.7%) *vs* $n=9$ (27%), $P = 0.005$), but more patients with pain as their presenting symptom ($n=24$ (65%) *vs* $n=6$ (18%), $P < 0.001$). Other symptoms were not significantly different. Presenting symptoms are presented in Table 2 and Figure 1. There was no difference between groups in the time between initial surgery and parastomal hernia diagnosis, or in EHS Classification(20).

Type of hernia repair and complications after hernia repair

Table 3 shows the different types of procedures performed for hernia repair. The vast majority of patients (72% in total) underwent open mesh repair. For two patients (25%) in the NT group, no specific records were available on the type of procedure. This was the only significant difference between the two groups.

An overview of the surgical complications is listed in Table 4. There were no statistically significant differences between the two groups; complication rates were 45% for ST and 50% for NT cross-overs ($P = 1.000$). Parastomal hernia recurrence occurred in 48% of all operated patients: in 23 (55%) ST patients and one (13%) NT cross-over patient ($P = 0.05$). Recurrences led to additional repair in 21 (50%) ST patients but in none of the NT patients ($P = 0.015$). Emergency surgery was needed for incarceration of the parastomal hernia in three patients (7.1%) in the ST group and one patient (13%) in the NT group. Detailed results regarding only those patients with end colostomy can be found in Supporting Information Tables S1 and S2.

Discussion

In this retrospective study of 80 patients with a parastomal hernia, the main reason for choosing NT over ST was absence of complaints (32%) and presence of comorbidities (24%). For 14 patients (37%), the reason for NT was not documented in the medical records. Although not documented, based on the baseline characteristics it could be that the initial oncologic surgery was a reason for NT in some of these patients. During a median follow-up of 46 months, eight patients (21%) crossed over from NT to ST. Cross-over, however, did not result in higher emergency surgery, postoperative complications or recurrence rates.

To date, few published data exist on outcomes of NT for parastomal hernia. There is one study from which no conclusions can be drawn because of its methodological flaws(18). However, data on NT for inguinal and incisional hernia are available(14-17). The data on inguinal hernia suggest that NT can be safe, whereas for incisional hernia cross-over to ST was associated with higher rates (29% *vs* 17%) of postoperative complications(17). Our study found higher postoperative complication rates in both groups (45% for ST and 50.0% for NT cross-overs). These figures are in accordance with literature data on parastomal hernia repair(21).

Apart from complications, the cumulated recurrence rate of both groups was 48%. Similar rates (6.9%-69.4%) are found in the literature(10). This demonstrates that parastomal hernia surgery is still not very successful. As long as these numbers remain this high, NT seems to be a feasible treatment option.

Limitations

The main limitation of this study is its retrospective design, which could potentially have introduced selection bias. NT strategy could have been chosen more often in patients with a worse general condition. This might be reflected in some of the baseline characteristics displayed in Table 1. However, it does not affect the results after hernia repair surgery in those patients who crossed over (Table 4).

It is possible that patients have visited other hospitals for ST (both elective and emergency surgery). Additionally, hernia characteristics and patients' complaints were not recorded systematically by surgeons or stoma nurses.

Secondly, we found a relatively small number of patients with parastomal hernia, given the study period and the number of participating hospitals. In our opinion, two possible explanations exist for this finding: (i) many patients with an asymptomatic parastomal hernia would not be referred to a hospital for this reason only and (ii) many parastomal hernias would not be diagnosed or registered during regular follow-up for patients' underlying disease. For these reasons, we can conclude that any missed patients were more likely to be treated conservatively. Moreover, patients who have surgery are more likely to have been identified because of that documentation in the patient records. Therefore, the NT group might in fact be larger and consequently cross-over rates might be lower than reported in this study. Finally, one important limitation in hernia research in general is the lack of data on patient-reported outcomes, such as quality of life and body image. Although they were reported as reasons for treatment choice, no patient-reported data were available on complaints after surgery and reasons for NT were missing in 37% of those cases. Therefore, the only outcome measures used to compare the two groups were parastomal hernia recurrence, postoperative complications, and emergency surgery rates.

To get more insight into the effects of different treatment options on patient-reported outcomes, prospective studies or registries should include these as outcome measures. Widely used generic quality of life questionnaires might not be able to distinguish between the effect of the underlying disease and the parastomal hernia itself. Therefore, disease-specific quality of life questionnaires concentrating on stoma-specific symptoms should preferably be used. Recently, an attempt has been made to develop such a questionnaire, which might be useful for future research (22). Furthermore, prospective research might be able to study more, possibly asymptomatic, patients with parastomal hernias, who are otherwise missed in retrospective reviews. Data from these future studies could support treatment recommendations for asymptomatic and symptomatic patients with a parastomal hernia.

In conclusion, despite the above mentioned limitations, this study is the first to provide insight into reasons, complications, and cross-over rates for NT compared to ST in patients with parastomal hernias. Based on the results, NT might be the better choice in patients without complaints or with comorbidities, since there is more potential for risk than benefit of ST in these patients.

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Tables

Table 1 Baseline patient characteristics

Characteristic	Surgical treatment (n=42)	Non-operative treatment (n=38)	P value
Age (SD)	51(15)	63 (12)	<0.001
Male (%)	17 (41)	22 (58)	0.179
BMI (SD)	27.65 (4.82)	26.02 (3.62)	0.101
Smoking (%)	10 (24)	7 (20)	0.786
COPD (%)	0 (0)	4 (11)	0.047
Corticosteroid use (%)	4 (9.5)	3 (7.9)	1.000
ASA Class (%)			0.169
I-II	37 (90)	20 (77)	
III-IV	4 (9.8)	6 (23)	
Indication of initial surgery (%)			
Malignancy	10 (24)	23 (62)	0.001
IBD	15 (37)	9 (24)	0.327
Other	16 (39)	5 (14)	0.020
Emergency surgery	11 (26)	10 (26)	1.000
ICU admission	6 (17)	7 (22)	0.760
Type of ostomy (%)			
End colostomy	23 (55)	26 (68)	0.254
Loop colostomy	2 (4.8)	0 (0)	0.495
End ileostomy	11 (26)	9 (24)	1.000
Loop ileostomy	2 (4.8)	1 (2.6)	1.000
Ileal conduit	4 (9.5)	2 (5.3)	0.678
Complications* (%)			
Surgical site infection	1 (2.9)	4 (12)	0.191
Abscess	2 (5.7)	5 (15)	0.259
Fistula	1 (2.9)	1 (3.0)	1.00
Ileus	4 (11)	2 (6.1)	0.675
Pneumonia	2 (5.6)	3 (9.1)	0.665
Other complications	7 (17)	4 (11)	
Follow-up time in months (IQR)	43.5 (20.3-72.0)	47.1 (28.5-96.2)	0.823

BMI, body mass index; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists; IBD, inflammatory bowel disease; ICU, intensive care unit; IQR, interquartile range. *Complications after initial surgery.

Table 2 Hernia characteristics

Characteristic	Surgical treatment (n=42)	Non-operative treatment (n=38)	P value
Size in cm (SD)	3.59 (1.96)	3.43 (1.37)	0.762
EHS Classification (%)			
I	17 (71)	12 (60)	0.532
II	4 (17)	6 (30)	0.472
III	1 (4.2)	2 (10)	0.583
IV	2 (8.3)	0 (0)	0.493
Time to diagnosis in months (IQR)	16.69 (5.67-38.05)	15.49 (4.90-31.63)	0.907
Presenting symptoms (%)			
No symptoms	1 (2.4)	9 (23.7)	0.011
Pain	24 (57)	6 (15.8)	<0.001
Appliance leakages	6 (14.3)	9 (23.7)	0.391
Bowel obstruction	4 (9.5)	6 (15.8)	0.505
Aesthetic complaints	1 (2.4)	2 (5.3)	0.602
Incarceration	1 (2.4)	1 (2.6)	1.000
Unknown	5 (12)	5 (13)	1.000

EHS, European Hernia Society; IQR, interquartile range

Table 3 Type of parastomal hernia surgery

Type of repair	Surgical treatment (n=42)	Non-operative treatment* (n=8)	P value
Open repair with mesh (%)	30 (72)	6 (75)	0.837
Open suture repair (%)	5 (12)	0 (0)	0.577
Restoration of continuity (%)	4 (9.5)	0 (0)	1.000
Stoma relocation (%)	3 (7.1)	0 (0)	1.000
Unknown (%)	0 (0.0)	2 (25)	0.023

*Cross-overs from non-operative treatment to surgical treatment.

Table 4 Complications after hernia repair

Complication	Surgical treatment (n=42)	Non-operative treatment† (n=8)	P value
Overall morbidity* (%)	19 (45)	4 (50)	1.000
SSI (%)	9 (21)	1 (13)	1.000
Seroma (%)	2 (4.8)	1 (13)	0.414
Obstruction (%)	2 (4.8)	0 (0)	1.000
Ileus (%)	3 (7.1)	1 (13)	0.514
Recurrence (%)	23 (55)	1 (13)	0.050
Additional repair (%)	21 (50)	0 (0)	0.015
Emergency surgery (%)	3 (7.1)	1 (13)	0.514
Follow-up time, in months (IQR)	43.5 (20.3-72.0)	55.0 (34.5-74.0)	0.700

SSI, surgical site infection; IQR, interquartile range.

*Number of patients with at least one complication.

†Cross-overs from non-operative treatment to surgical treatment

Figures

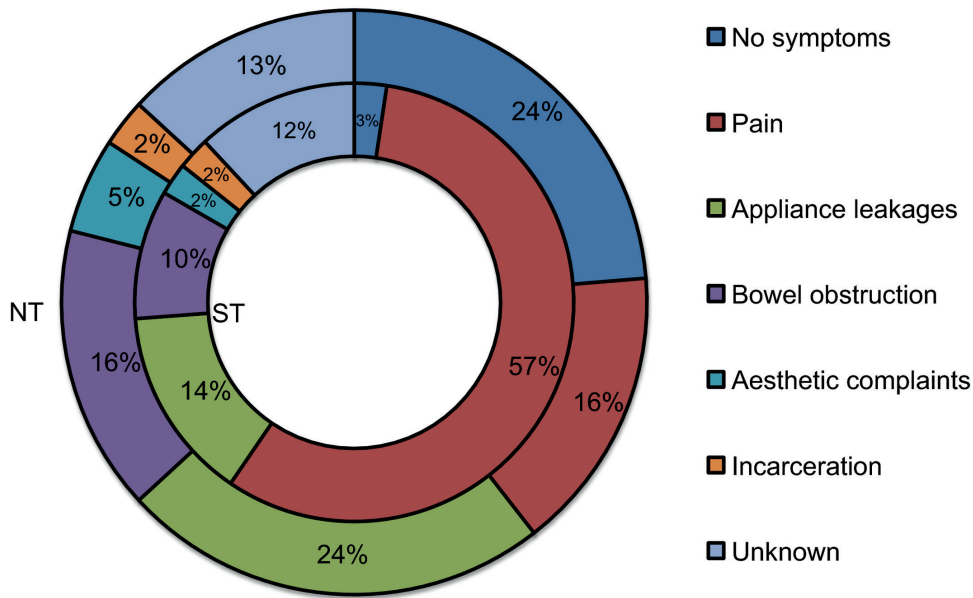


Figure 1 Parastomal hernia symptoms
The outer circle represents the non-operative treatment (NT) group, the inner circle represents the surgical treatment (ST) group.

Supporting Information

Supplemental Table 1 Hernia characteristics in end colostomy patients

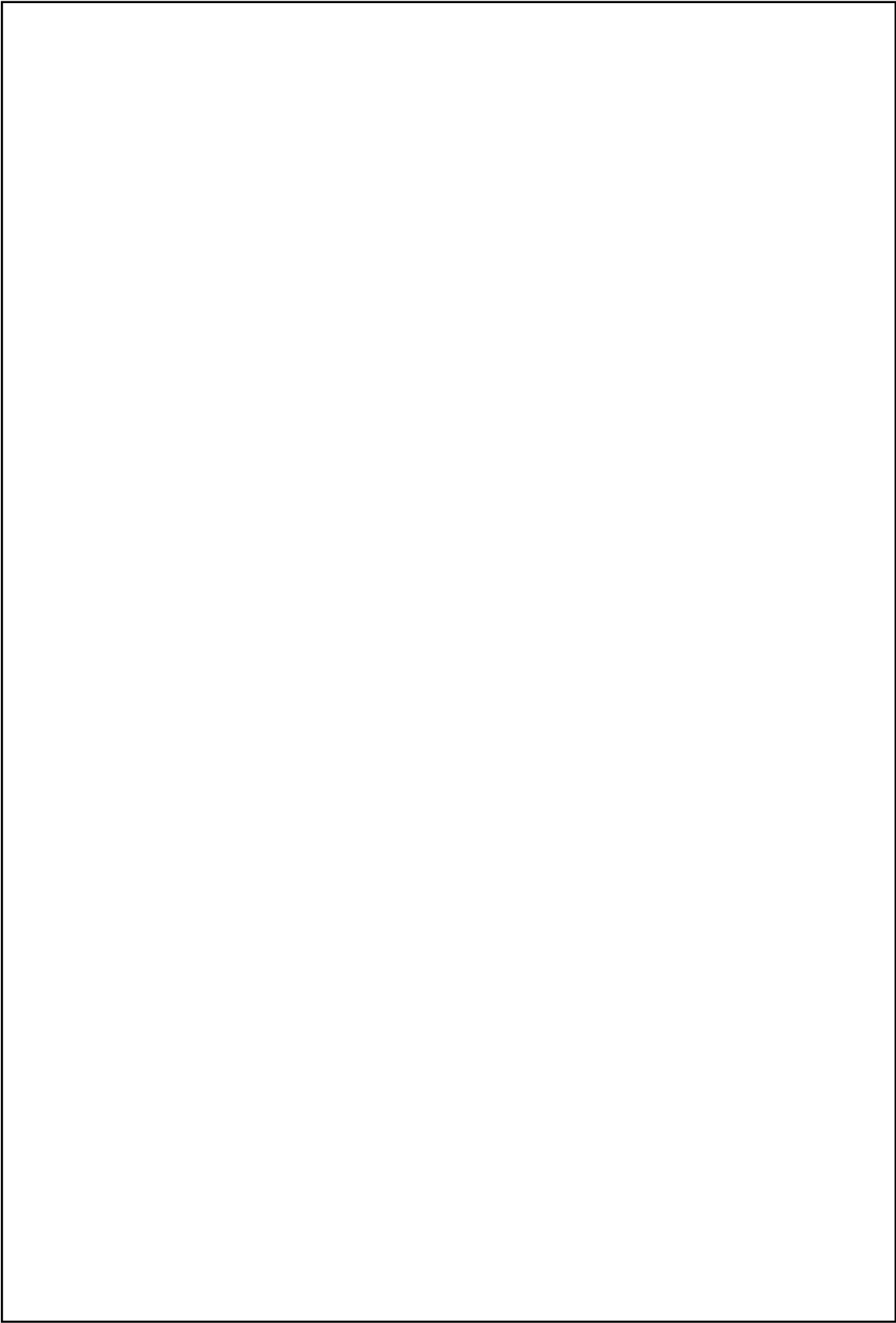
Characteristic	Surgical treatment (n=23)	Non-surgical treatment (n=26)	P-value
Size in cm (SD)	3.48 (1.84)	3.10 (1.26)	0.537
EHS Classification (%)			
I	9 (64.3)	7 (58.3)	0.756
II	4 (28.6)	4 (33.3)	1.000
III	0 (0)	1 (8.3)	0.462
IV	1 (7.1)	0 (0)	1.000
Time to diagnosis in months (IQR)	12.50 (3.92-26.32)	13.47 (4.35-27.03)	0.772
Presenting symptoms (%)			
No symptoms	1 (4.8)	6 (28.6)	0.093
Pain	16 (76.2)	5 (23.8)	0.001
Appliance leakages	2 (9.5)	6 (28.6)	0.238
Bowel obstruction	2 (9.5)	3 (14.3)	1.000
Aesthetic complaints	0 (0)	1 (4.8)	1.000
Incarceration	0 (0)	0 (0)	NA

SD, standard deviation; EHS, European Hernia Society; IQR, interquartile range

Supplemental Table 2 Complications after hernia repair in end colostomy patients

Complication	Surgical treatment (n=23)	Non-surgical treatment (n=5)	P-value
Overall morbidity (%)	10 (43.5)	2 (40.0)	1.000
SSI (%)	5 (21.7)	0 (0)	0.550
Seroma (%)	0 (0)	1 (20.0)	0.179
Obstruction (%)	2 (8.7)	0 (0)	1.000
Ileus (%)	2 (8.7)	1 (20.0)	0.459
Recurrence (%)	14 (60.9)	0 (0)	0.041
Additional repair (%)	13 (56.5)	0 (0)	0.044
Emergency surgery (%)	1 (4.3)	1 (20.0)	0.331
Follow-up time in months (IQR)	41.00 (24.00-61.00)	60.00 (47.50-86.87)	0.041

SSI, surgical site infection; IQR, interquartile range



Chapter 11

Comparison of different modalities for the diagnosis of parastomal hernia: a systematic review

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International Journal of Colorectal Disease (2020): 1-14

Abstract

Purpose

Parastomal hernia (PSH) is a common complication following stoma formation. The incidence of PSH varies widely due to several factors including differences in diagnostic modality, observer, definition and classification used for diagnosing PSH. The aim of this systematic review was to evaluate the diagnostic accuracy of the modalities used to identify PSH.

Methods

Embase, MEDLINE, Cochrane, Web of Science and Google Scholar databases were searched. Studies reporting PSH incidence rates detected by two or more different diagnostic modalities or inter-observer variation on one diagnostic modality were included. Article selection and assessment of study quality were conducted independently by two researchers using Cochrane Collaboration's tool for assessing risk of bias. PROSPERO registration: CRD42018112732.

Results

Twenty-nine studies ($n = 2514$ patients) were included. Nineteen studies compared CT to clinical examination with relative difference in incidence rates ranging from 0.64 to 3.0 ($n = 1369$). Overall, 79% of studies found an increase in incidence rate when using CT. Disagreement between CT and clinical examination ranged between 0 and 37.3% with pooled inter-modality agreement Kappa value of 0.64 (95% CI 0.52–0.77). Four studies investigated the diagnostic accuracy of ultrasonography ($n = 103$). Compared with peroperative diagnosis, CT and ultrasonography both seemed accurate imaging modalities with a sensitivity of 83%.

Conclusion

CT is an accurate diagnostic modality for PSH diagnosis and increases PSH detection rates, as compared to clinical examination. Studies that specially focus on the diagnostic accuracy are needed and should aim to take patient-reported outcomes into account. A detailed description of the diagnostic approach, modality, definition, and involved observers is prerequisite for future PSH research.

Introduction

Parastomal hernia (PSH) is a common complication following stoma formation and can cause discomfort, pain, strangulation, and incarceration of intestines, as well as difficulties with stoma care (1). The exact incidence of PSH remains unclear, but most studies report high rates of over 30%, especially in case of colostomy (1, 2). Still, reported rates vary widely in the literature, ranging from 0-86% (1, 3, 4). This variability depends on several factors such as the length of follow-up, patient and surgical characteristics including type of stoma, method of stoma construction, but also on definition of PSH (5-8).

Moreover, several different diagnostic modalities can be used for the diagnosis of PSH, making it a factor affecting the incidence rate. In practice, clinical examination is the first method to assess the presence or absence of a PSH. In case of doubt about the diagnosis or to help plan for the surgical approach and management, an imaging modality can be chosen, such as ultrasonography (US), computed tomography (CT) scan, or magnetic resonance imaging (MRI) scan.

In addition, the lack of a clear definition and the use of several different classifications of PSH is a significant problem in PSH research (9). Some studies use imaging to confirm the diagnosis of PSH, whereas others only use imaging in clinically unconvincing cases (10, 11). Due to these differences, protocols often deviate between clinical practice and the research setting, as well as between clinical studies.

In 2014, the European Hernia Society (EHS) proposed a classification depending on the defect size and the presence of a concomitant incisional hernia (9, 12). With the ability to correctly compare different studies and thus to provide a uniform research reporting, this classification is recommended by the EHS to use in PSH research (9). However, these guidelines also emphasize the uncertainties on the accuracy of clinical and imaging diagnoses of PSH.

Therefore, the aim of this systematic review is to evaluate the accuracy of the different modalities used to identify PSH after stoma construction or after PSH repair. The secondary objective is to assess the inter-observer variation, correlations between (a) symptomatic PSH and imaging or surgical findings, and identify different definitions and classifications used for diagnosis of PSH.

Methods

The study protocol was registered in PROSPERO (CRD42018112732; International Prospective Register of Systematic Reviews). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) statement was followed (13). Moreover, the article by Wille-Jørgensen *et al.* on systematic reviews and meta-analyses in coloproctology was used for methodological guidance (14).

Systematic literature search

A systematic search was performed by a biomedical information specialist instructed by first author (G.S.). Embase, MEDLINE, Cochrane, Web of Science and Google Scholar databases were searched on March 5th, 2019. Full search strategies and results per database are presented in Appendix 1. There was no limit on date of publication. After duplicate removal, studies were reviewed independently by two researchers (D.L. and G.S.) on title and abstract, followed by full-text review using EndNote X9®. Differences in article selection were discussed and articles were included or excluded after consensus was reached.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) Inclusion of patients that underwent stoma construction (ileal conduit, ileo- or colostomy) or PSH repair surgery; (2) Studies assessing the performance of a diagnostic modality (clinical examination, CT, US, MRI or diagnosis at surgery) used for the diagnosis of PSH. Only (non) randomized controlled trials, prospective, or retrospective cohort or case-control studies were included. Excluded were: Studies reporting on pediatric patients (< 18 years of age), studies reporting only on gastro-/oesophago- or duodenostomies, studies in which no data on diagnostic modalities were described, and studies with unclear diagnostic work-up, so that diagnostic data could not be extracted. Studies not written in English, case reports, letters, comments, abstracts or posters were also excluded.

Data extraction

Data from included studies were extracted by one researcher (G.S.) and were checked independently by another researcher (S.H.) using standard forms covering study characteristics (year, journal, study design, level of evidence and risk of bias), patient characteristics (number of patients, sex, age, body-mass index and follow-up), surgical characteristics (indication for surgery, acute or elective, laparoscopic or open abdominal surgery, reoperation, stoma type, use of mesh, location of mesh), and outcome characteristics (definition and classification of PSH, diagnostic modalities and corresponding incidence of PSH and inter-observer variation). Since there is no gold standard modality for diagnosing a PSH, the detection rates of the different diagnostic modalities are compared within each study. The available absolute data and incidence rates of modalities are presented and compared in contingency tables. Intra-class correlation coefficient and Kappa values for inter-observer variation were extracted and presented. Inter-modality agreements were expressed as Cohen's Kappa values for each study if possible. Statistical level of agreement per Cohen's Kappa value range is presented in Supplemental table 1. The pooled Cohen's Kappa value was calculated in a

random effects model using inverse variance method, using meta-package for R version 3.5.1. (R Foundation for Statistical Computing, Vienna, Austria).

Study quality assessment

Two researchers (S.H. and G.S.) independently assessed the quality of included studies by assessing the level of evidence according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (15) and the possible risk of bias using the Cochrane Collaboration's tool for assessing risk of bias (16) and the QUADAS-2 tool (17) with RevMan 5.3 (Cochrane Centre, Denmark).

Results

Search and study characteristics

A PRISMA flow diagram of the complete search results is shown in Figure 1. After removal of duplicates, 1,495 articles were screened on title and abstract of which 192 articles were selected for full-text reading. Finally, 29 articles were judged eligible and were included.

An overview of study characteristics is shown in Table 1. The methodological quality of all included studies per outcome measure is summarized in Figure 2. Overall, a high risk of bias was present in the included studies (Figure 3). Applicability concerns were present in 10-20% of the review sample (Figure 3). Specific methodological concerns per included study are outlined in Appendix 2.

Definition and classification of PSH

The definition of PSH was reported in eighteen (62%) of the included studies (2, 11, 18-32). Some studies used two different definitions for clinical and radiologic examination (19, 20, 23, 25). Therefore, a total of nineteen different definitions were used (Appendix 3). For the definitions used in clinical examination, most studies included a combination of the terms 'bulge' or 'protrusion' and 'around' or 'in the vicinity of' the stoma. Also, some studies added the position of the patient's body (supine or/and erect) during examination and the use of the Valsalva maneuver. For the definitions used in radiological examination, the terms 'defect,' 'fascia' and 'hernia sac' were often incorporated in the definition. Five studies did not describe the definition of PSH or diagnostic approach (33-37).

The classification of PSH was reported in thirteen (45%) of the included studies (2, 10, 21, 26, 28, 31, 32, 38-43). Two classifications were used. One developed and introduced by the European Hernia Society (12) and one by Moreno-Matias (26) (Appendix 4).

Inter-observer variation

Three of the included studies reported on inter-observer variation (22, 25, 30). Each study investigated different modalities examined by different observers. An overview of the methods and results of these studies is summarized in Table 2. Gurmu *et al.* reported a low inter-observer reliability when diagnosing PSH by clinical examination

with disagreement rates of 35 and 54% between three surgeons and 18% between two surgeons (22). Jänes *et al.* reported a strong agreement between three surgeons after diagnosing PSH by clinical examination with a Kappa value of 0.85 (25). Also, the inter-observer reliability was higher amongst radiologists when patients underwent a CT in prone position as compared to patients in supine position with Kappa values of 0.85 and 0.82, respectively (25). Strigård *et al.* investigated inter-observer reliability and learning curve of three-dimensional ultrasonography (3D US) in 40 patients. They found an overall inter-observer agreement of 72% with a Kappa value of 0.59, which is classified as 'weak'. The learning curve reached its top at around 30 patients with an inter-observer agreement of 80% for the last ten examined patients (30).

CT versus clinical examination

The incidence rates of PSH after CT and clinical examination were reported in nineteen studies including a total of 1,369 patients (2, 18-20, 23, 24, 27, 28, 31-33, 37-41, 43). PSH incidence rates, disagreement percentages, and Kappa values are presented in Table 3. Study quality and clinico-radiological concordance are presented in Supplemental table 2. Fifteen studies (79%) reported a higher incidence rate and two studies (11%) reported lower incidence rate when diagnosing PSH using CT as compared to clinical diagnoses. When comparing CT to clinical examination, the relative difference in incidence rates ranged from 0.64 to 3.0. Disagreement between diagnoses by using CT versus clinical examination could be obtained in fifteen studies and ranged from 0 to 37.3%. The pooled inter-modality agreement Kappa value for all fourteen studies with contingency tables was 0.64 (95% CI 0.52-0.77) which is classified as 'substantial agreement'.

Ultrasonography versus clinical examination

The incidence rates of PSH after US and clinical examination were reported in one study, which included 43 patients with peristomal bulging (Table 4, Supplemental table 3) (29). Sjö Dahl *et al.* reported a lower incidence rate by US for diagnosing PSH with relative difference of 0.58 when compared to clinical examination. The disagreement between these modalities was 53.5%.

CT versus ultrasonography

Studies comparing PSH incidence of CT to regular US were not identified. One study by Näsvalld *et al.* (36), investigated intrastomal 3D US as an alternative to CT and included twenty patients that were indicated for surgical revision due to stoma-related symptoms. The PSH incidence was higher when using CT (80%) as compared to 3D US (75%) (Table 5, Supplemental table 4).

Peroperative diagnosis

Näsvalld *et al.* compared 3D US and CT to findings at surgery in twenty patients (36). For both imaging modalities a high sensitivity of 83% was found. A positive predictive value (PPV) of 94% and a negative predicted value (NPV) of 75% were reported for diagnosis with CT. For diagnosis with 3D US, a PPV of 100% and a NPV of 60% were reported. Also, Fleshman *et al.* reported peroperative findings in thirteen patients who were diagnosed with PSH at clinical examination of which eleven were confirmed

by CT and two were confirmed operatively (34). Study quality, PSH incidence rates and surgico-radiological concordance of the two studies are presented in Table 6 and Supplemental table 5.

Imaging versus clinical examination

Two studies reported on clinical examination, CT and MRI for the diagnosis of PSH. These studies did not subdivide the incidence rate per type of imaging modality (11, 21). Study quality, PSH incidence rates and clinico-radiological concordance of the studies are presented in Table 7 and Supplemental table 6. Donahue *et al.* reported a higher incidence rate when using imaging with a relative increase of 1.47 and found no patients with clinical detected but radiological occult PSH (21). Hansson *et al.* found three symptomatic PSHs in 60 patients that were clinically examined. A CT or MRI was performed in 27 of the 60 patients of whom nineteen patients had a asymptomatic hernia. Hotouras *et al.* reported 25 (58%) PSHs diagnosed with CT. Eleven (44%) of these 25 patients with radiological confirmed PSH were symptomatic as reported by the patients.

Imaging after clinical suspicion of parastomal hernia

Brandsma *et al.* and Fleshman *et al.* used only a CT when there was clinical suspicion of PSH. In the study of Brandsma *et al.* (10), sixteen out of nineteen clinical PSHs (14.3%) were confirmed by CT, two by MRI and one by US. Fleshman *et al.* found thirteen (13%) clinical PSHs of which eleven (11%) were confirmed by CT and two peroperatively. Hansson *et al.* performed a CT or MRI when there were doubts about the diagnosis of PSH during clinical examination (11). One participating center performed imaging routinely (Table 7). The incidence after clinical examination was 5% (3/60) and after imaging 7% (4/61).

Discussion

Today, in both clinical practice and research there is no gold standard modality to examine patients for the presence of PSH. The literature on this subject is diverse and inconclusive. Facilitating comparison between studies on PSH remains challenging, due to, amongst others, the number of existing definitions, imaging modalities, and classifications. Indeed, this systematic review shows a great variance in detection rates of PSH between different diagnostic modalities.

Most included studies compared CT to clinical examination. The majority of these studies found higher incidence rates by using CT (2, 18-20, 24, 26-28, 32, 33, 38, 40-43). However, some studies showed contradictory results in favor of clinical examination (23, 34, 39). This discrepancy between studies could be explained by the technical differences in examination of the patients' abdominal wall, bearing in mind that a patients' body position and the use of Valsalva maneuver during examination might affect detection rates (25). It is possible to use Valsalva maneuver in case of patients undergoing CT imaging. However, this is rarely reported in studies.

Gurmu *et al.* found a low inter-observer reliability when patients were clinically examined by surgeons, indicating that PSH is difficult to diagnose by clinical examination (22). This was also stated by Sjö Dahl *et al.* who found poor correlation between US and findings at clinical examination (29). If these examinations are performed correctly, the use of dynamic modalities such as US and clinical examination may have some advantages compared to the more static and expensive CT or MRI. However, the inter-observer variation and diagnostic accuracy of US have not been investigated thoroughly. In contrast, more evidence is available on the diagnostic performance of clinical examination and CT. For research purposes, the combined use of these two modalities might be recommended since multiple studies found significant disagreements in detection rates between both modalities (23, 26, 32).

This is the first review to date that provides a complete overview of the research of the available literature on different diagnostic modalities for PSH diagnosis. Nevertheless, it is important to note that this systematic review covers studies that investigate the PSH incidence rates in the setting of a research protocol that might not always fully reflect standard clinical practice. Also, the minority of included studies has the accuracy of the used diagnostic modality as primary outcome (19, 22, 25, 26, 29, 30, 33, 36). In clinical practice the main goal is to identify symptomatic PSHs that might require treatment and for asymptomatic patients it seems unnecessary to follow a full diagnostic workup. Therefore, the clinical approach might differ from that in a research setting. In general, patients with stoma problems such as pain, appliance leakage, bowel obstruction or symptoms of incarceration, first undergo clinical examination by a stoma nurse and/or clinician. When PSH is identified clinically or the diagnosis is inconclusive the clinician can consider an imaging modality to confirm the diagnosis, taking into account patient safety, patient comfort, availability and costs. Whereas for research purposes, factors as costs and availability might play a less important role in the decision on imaging modality.

Intrastomal 3D US is a relatively new imaging modality for diagnosing PSH or other stoma-related pathology (44). 3D US seems to be an accurate imaging modality with a sensitivity of 83% when compared to peroperative diagnosis (36). With this imaging modality it is possible to examine patients in erect position and without the use of radiation, providing potential advantages over CT. There is, however, too little available evidence for this technique to consider this as standard imaging modality for the diagnosing of PSH.

In contrast to diagnosing incisional hernia, traditional two-dimensional ultrasonography (2D US) is not often used for diagnosing PSH in both research and in clinical setting. However, 2D US is the most patient-friendly, inexpensive and practical modality of all imaging modalities. This systematic review included only one study comparing 2D US to clinical examination for diagnosing PSH. However, to make any recommendations on 2D US, it would be interesting to compare ultrasonography with other imaging modalities in the future.

Another important aspect of clinical practice with regard to the use of diagnostic modalities is that many stoma patients have a stoma created after oncological resection and for these patients a CT is routinely made during follow-up to detect potential cancer recurrence. Although some PSHs occur many years after stoma construction, most PSHs develop within the first years after stoma construction and are thus likely to be identified with follow-up CT (5). This is one of the main reasons why most included studies used CT instead of MRI or US. However, with the patient in supine position a CT is not a reliable tool for diagnosing PSH and a CT with the patient in prone position is associated with higher inter-observer agreement and an increase in sensitivity (25). By using CT routinely for cancer follow-up, asymptomatic PSHs will appear more frequently. Although not entirely insignificant, studies do not often distinguish between symptomatic and asymptomatic when reporting PSH incidence rates.

Evidently, patient-reported outcomes are of paramount importance in the context of stoma-related complications. Patients know their own bodies in a way no physician possibly can, and have to take care of the stoma several times a day, whereas the physician examines the patients' stoma once or maybe twice. Any physical differences of the stoma will be noticed by the patient, which probably makes it more reliable than the studied modalities on the existence of bulging at some time point during follow-up. Currently, prospective cohort studies, such as the PROPER and CIPHER studies (ISRCTN17573805; ISRCTN registry), are assessing the value of subjective and objective outcomes after stoma construction or for parastomal hernia treatment, respectively.

Despite the increased interest in PSH care and research in recent decades, there is still no consensus regarding the definition of PSH or a gold standard for diagnosis (9). Although many definitions consisted of similar terms and contexts, some definitions differ considerably which can lead to discrepancies in detection rates. Moreover, the fact that five included studies have not even described the definition of PSH, emphasizes the need for uniform reporting in studies regarding PSH (33-37). This heterogeneity in diagnostic procedures makes it difficult to compare studies and to determine an accurate incidence of PSH. Therefore, a clear and standard definition and diagnosis of PSH is of paramount importance. The European Hernia Society (EHS) acknowledged this problem and proposed to use the definition of PSH introduced by Muysoms *et al.* (45): "An incisional hernia through the abdominal wall defect created during placement of a colostomy, ileostomy or ileal conduit stoma". Furthermore, the EHS proposed a new classification for PSH, which might help to facilitate more uniform reporting of outcomes in PSH research (Appendix 4) (12).

Limitations

This systematic review has some limitations. Firstly, the low level of evidence of included studies is an important limitation. Eleven studies have a retrospective study design, which is prone for selection and information bias. Also, most studies presented small study populations. Nevertheless, to give a complete overview of diagnostic accuracy and variation of the different modalities, studies of low quality or studies with small samples

were not excluded and a comprehensive overview of study characteristics and study quality assessment was provided.

Secondly, significant heterogeneity between studies was demonstrated, as operation and stoma types, use of mesh reinforcement, patient characteristics (e.g. age and BMI), and follow-up duration differed between included studies. Besides the choice of diagnostic modality, all these factors also influence the PSH incidence rates. Although it was not possible to account for this, these factors would be of less importance for the within-study diagnostic performance, since diagnostic modalities were only compared within each study. However, some studies did not investigate the PSH incidence rate or the accuracy of the diagnostic modalities as primary objective. As a result, the incidence could easily be underestimated. Accordingly, the results of diagnostic performance may also be affected.

Conclusion

In conclusion, this review shows great variance in accuracy of different modalities for the detection of PSH. The use of CT increases the PSH detection rate, indicating that this is a more accurate modality compared to clinical examination. However, the evidence on the accuracy of the other imaging modalities, also within patient-reported outcome measures, is scarce and warrants further investigation. There are significant differences in diagnostic methods between clinical practice and in the setting of research protocols, as well as between clinical studies. In order to compare studies correctly and increase transparency among studies, a more detailed report of the diagnostic method and a detailed and preferably uniform definition are required in future research. It might be of added value to develop a standard and validated protocol in which self-report, clinical examination and imaging are combined.

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Table 1 Overview of included studies.

Study	Modalities included	Surgical procedure	N	Stoma type	Age in years	BMI (kg/m ²)	Follow-up in months
Aslam	CE, CT	Colorectal cancer, open and laparoscopic	19	C	67	~	12
Brandtsma	CT, MRI, US	Abdominal open	150	EC	mesh: 63.5 no mesh: 63	mesh: 26.8 no mesh: 26.5	12
Canda	CE, CT	Colorectal cancer, open and laparoscopic	67	EC	SMART: 59 (13) control: 55 (14)	SMART: 26.2 (4.8) control: 26.5 (5.3)	27 (12-41)
Cingi	CE, CT	~	23	16 EC, 5 LC, 2 I	PSH: 59.2 no hernia: 56.4	PSH: 27.3 (4.2) no hernia: 25.5 (6.8)	15 (2-63)
Conde-Muino	CE, CT	Abdominal	31	EC	63	>30 (23%), <30 (77%)	17.5 (12-43)a
Donahue	CE, CT or MRI	Abdominal open	386	U	74 (68-79)	27.7 (24.5-31.5)	12
Etherington	CE, CT	Inflammatory bowel disease, open	28	I	24-89	~	~
Fleshman	CE, CT, surgery	Abdominal open and laparoscopic	113	75 EC, 42 EI	PADM: 60.3 (13.6) control: 59.1 (14.4)	PADM: 26.2 (4.6) control: 24.7 (4.1)	24
Gurmu	CE, CT	Colorectal cancer	41	41 EC	~	25.8	60 (48-120)
Hansson	CE, CT or MRI	Abdominal laparoscopic ¹ conversion	61	55 C, 4 I, 2 U	63 (36-83)	30.9 (18.6-51)	26
Hauters	CE, CT	Colorectal cancer, open and laparoscopic	29	EC	73 (39-88)	28 (21-43)	48 (6-88)
Hino	CE, CT	Abdominal laparoscopic	59	EC	73 (45-86)	22.5 (14.9-43)	21 (2-95)
Hong	CE, CT	Abdominal	108	EC	60.1 (33-86)	23.9 (16.4-36.6)	25 (6-73)
Horouras	CT	Abdominal	43	EC	69	PSH: 26.9 (20-36) no hernia: 23.5 (22-30)	PSH: 26 no hernia: 16
Ihnát	CE, CT	Colorectal cancer, open and laparoscopic	148	EC	63.1 (0.68)	26.8 (0.34)	24

Study	Modalities included	Surgical procedure	N	Stoma type	Age in years	BMI (kg/m ²)	Follow-up in months
Jänes	CE, CT	Colorectal cancer	27	EC	-	-	-
Köhler	CE, CT	Abdominal open and laparoscopic	80	7/4 C, 6 I	71.4 (46-91)	26.4 (18.4-36.8)	21 (3-47)
Lambrecht	CE, CT	Abdominal open	58	EC	mesh: 64 no mesh: 63	mesh: 24.6 no mesh: 25.5	mesh: 36 no mesh: 48
Moreno-Matias	CE, CT	Abdominal	75	EC	72.5	27.2	-
Näsvall	CT, 3D US, surgery	Abdominal	20	14 C, 2 I, 4 U	67 (19-91)	26 (18-35)	-
Näsvall	CE, CT	-	50	33 C, 8 I, 9 U	72 (23-93)	26.8 (15.6-37.7)	12
Nikberg	CE, CT	Colorectal cancer	206	EC	mesh: 70 (48-88) no mesh: 72 (38-88)	mesh: 26 (19-36) no mesh: 25 (17-37)	31 (12-202)
Odensten	CE, CT	Colorectal cancer	232	C	mesh: 69.7 (41-86) no mesh: 69.9 (35-89)	mesh: 26.1 (16.7-37.8) no mesh: 26.3 (18.5-43.7)	12
Seo	CE, CT	-	83	EC	66 (22-80)	23.5 (17.5-36.6)	30 (6-45)
Serra-Aracil	CE, CT	Colorectal cancer, open	54	EC	mesh: 67.5 (8.8) no mesh: 67.2 (9.7)	mesh: 25.6 (2.9) no mesh: 27.3 (3.5)	29 (13-49)
Sjödahl	CE, US	-	63	C	69 (28-90)	-	68 (3-426)
Strigård	CE, 3D US	-	40	C and I	-	all patients < 35	-
Timmermans	CE, CT	Colorectal cancer, open	150	EC	67.4 (10.2)	25.9 (5.1)	49 (30-75)
Veirima	CE, CT	Colorectal cancer, laparoscopic	70	EC	mesh: 67.1 (10.7) no mesh: 65.1 (11.7)	mesh: 26.2 (4.6) no mesh: 25.4 (4.3)	12

Continuous data are median (interquartile range), mean (standard deviation) or mean (standard deviation, range).

CE, clinical examination; CT, computed tomography scan; MRI, magnetic resonance imaging; US, ultrasonography; SMART, stapled mesh stoma reinforcement technique; PSH, parastomal hernia; PADM, porcine-derived acellular dermal matrix; C, colostomy; I, ileostomy; EC, end colostomy; EI, end ileostomy; LC, loop colostomy; U, urostomy.

^a CT and CE at 12 months follow-up.

Table 2 Inter-observer variation.

Gurmu	Risk of bias	+++				Kappa
	Level of evidence	2b	Hospital I, 3 surgeons, n = 17	35		0.35-0.64
	Panel of 5 surgeons, clinical examination ^a		Hospital II, 3 surgeons, n = 13	54		0.29-0.43
			Hospital III, 2 surgeons, n = 11	18		0.73
Jänes	Risk of bias	+++	N = 27			Kappa
	Level of evidence	2b	3 Surgeons, clinical examination			0.85
	6 Observers: 3 surgeons and 3 radiologists		3 Radiologists, CT in prone position			0.85
			3 Radiologists, CT in supine position			0.82
Strigård			Surgeons and radiologists collectively, CT in prone position			0.80
			Surgeons and radiologists collectively, CT in supine position			0.64
	Risk of bias	+		Disagreement (%)		Kappa
	Level of evidence	2b	3 Investigators, n = 17	41		-
	Panel of 3 physicians, 3D ultrasonography		2 Investigators, n = 40	20		-
			Combined	28		0.59

^a Choosing between: hernia, bulge or no hernia.

Table 3 CT versus clinical examination.

Study	N	Incidence CT vs CE (%)	Relative increase with CT	Disagreement CE vs CT (%)	Kappa value	Standard Error	95% CI
Aslam	17	CT: 18%, CE: 18%	1	0	1	0.00	1.00-1.00
Canda	67	CT: 28%, CE: 22%	1.27	6	0.84	0.08	0.69-0.99
Cingi	21	CT: 86%, CE: 52%	1.5	28.6	0.36	0.22	0.00-0.79
Conde-Muino	31	CT: 7%, CE: 3%	2	3.2	0.65	0.34	0.00-1.00
Eheringron	28	CT: 36%, CE: 29%	1.25	11.1	0.84	0.11	0.62-1.00
Hauters	29	CT: 7%, CE: 3%	2	3.5	0.65	0.34	0.00-1.00
Hino	59	CT: 17%, CE: 20%	0.93	37.3	0.25	0.13	0.00-0.50
Hong	108	CT: 27%, CE: 33%	1.24	6.5	0.85	0.06	0.74-0.96
Köhler	51	CT: 4%, CE: 1%	3	3.9	0.49	0.36	0.00-1.00
Lambrecht	58	CT: 33%, CE: 24%	1.36	22.4	0.45	0.13	0.19-0.72
Moreno-Matias	75	CT: 47%, CE: 44%	1.06	29.3	0.41	0.11	0.20-0.62
Näsvall	47	CT: 15%, CE: 22%	0.64	17	0.46	0.17	0.11-0.80
Seo	83	CT: 29%, CE: 24%	1.2	4.8	0.88	0.06	0.76-0.99
Serre-Aracil	54	CT: 33%, CE: 28%	1.2	5.56	0.87	0.07	0.73-1.00
Veirimaa	67	CT: 49%, CE: 25%	1.94	23.9	0.52	0.10	0.31-0.72
Fleshman	~	CT: 11%, CE: 13%	~	~	~	~	~
Ihnát	148	CT: 53%, CE: 48%	~	~	~	~	~
Nikberg	187 (141 CT)	CT: 53%, CE: 25%	~	~	~	~	~
Odensten	211 (198 CT)	CT: 35%, CE: 29%	~	~	~	~	~
Timmermans	150 (87 CT)	CT: 53%, CE: 53%	~	~	~	~	~
Pooled Kappa value, random effects model					0.64		0.52-0.77

CE, clinical examination; CT, computed tomography scan.

Table 4 Ultrasonography versus clinical examination.

Study	N	Incidence US vs CE (%)	Relative increase with US	Disagreement CE vs US (%)	Kappa value	Standard Error
Sjödahl	43	US: 35%, CE: 61%	0.58	53.5%	-0,01	0,94

CE, clinical examination; US, ultrasonography.

Table 5 CT versus ultrasonography.

Study	N	Incidence CT vs 3D US (%)	Relative increase with US	Disagreement CT vs US (%)
Nasväll	20	CT: 80%, US: 75%	~	~

CT, computed tomography scan; US, ultrasonography.

Table 6 Peroperative diagnosis.

Study	N	Incidence CT vs surgery (%)	Incidence US vs surgery (%)	Disagreement imaging vs surgery (%)
Nasväll	20	CT: 80%, surgery: 90%	~	20%
Fleshman	~	CT: 11%, surgery: 13%	~	~
Nasväll	20	~	US: 75%, surgery: 90%	15%

CT, computed tomography scan; US, ultrasonography.

Table 7 Imaging versus clinical examination.

Study	N	Incidence imaging vs CE (%)	Relative increase with imaging	Disagreement imaging vs CE (%)	Kappa value	Standard Error
Donahue	386	Imaging: 36%, CE: 24%	1.47	15	0.73	0,04

CE, clinical examination

Figures

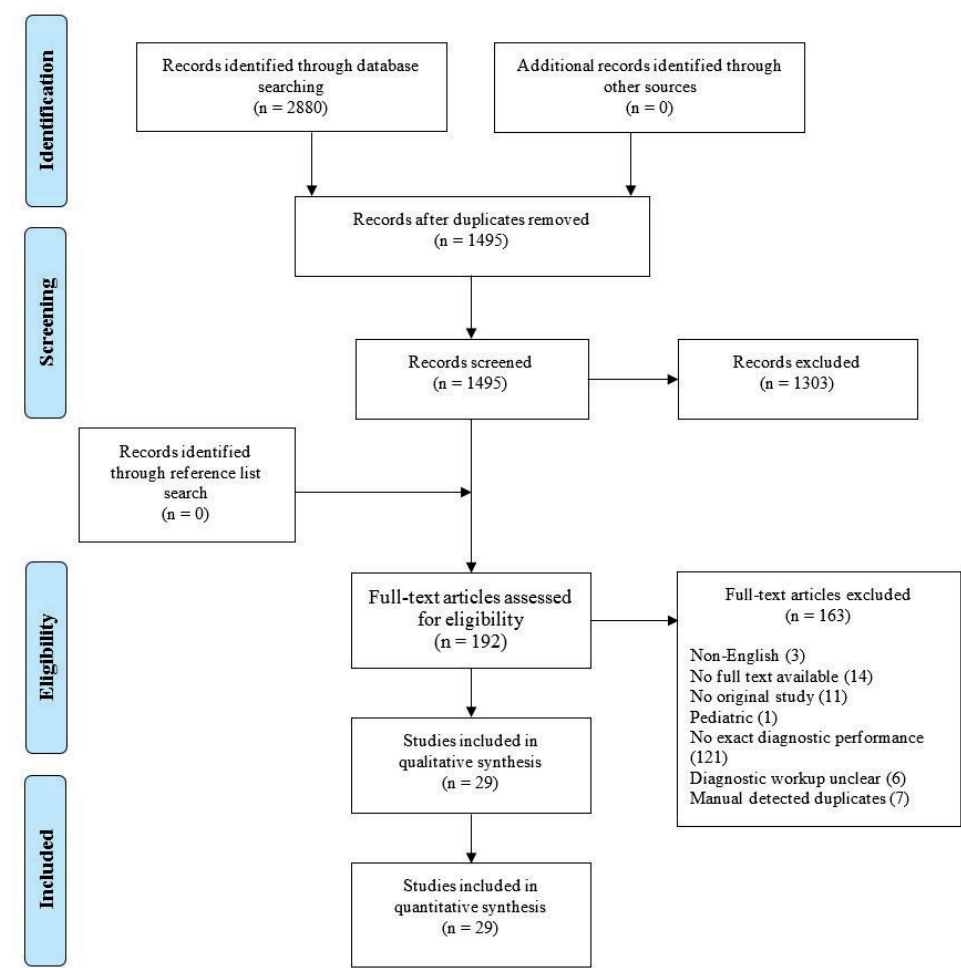


Figure 1 Preferred items for reporting of systematic reviews and meta-analyses (PRISMA) flow diagram.

		Risk of Bias				Applicability Concerns		
		Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Inter-observer variation	Gurmu 2011	+	+		+	+	+	
	Jänes 2011	+	+		+	+	+	
	Strigard 2013	-	?		+	+	+	
CT-scan vs clinical examination	Aslam 2019	+	-	?	+	+	+	?
	Brandsma 2017	-	+	+	-	-	+	+
	Canda 2018	-	-	?	+	+	+	+
	Cingi 2006	+	?	?	-	+	+	+
	Conde-Muino 2017	+	+	+	+	+	+	+
	Etherington 1990	+	-	+	+	+	+	+
	Fleshman 2014	-	-	?	-	-	+	+
	Hauters 2016	+	?	?	+	+	+	+
	Hino 2017	+	?	+	+	+	+	+
	Hong 2013	+	-	?	+	+	?	+
	Ihnát 2018	?	+	+	+	+	+	+
	Köhler 2016	-	?	?	-	?	+	+
	Lambrecht 2015	+	+	+	+	+	+	+
	Moreno-Matias 2009	+	+	+	+	+	+	+
	Näsvall 2017	-	?	?	-	+	-	+
	Nikberg 2015	-	?	?	-	+	?	+
	Odensten 2017	-	+	+	-	+	+	+
	Seo 2011	+	+	?	?	+	+	?
	Serra-Aracil 2009	+	+	?	+	+	+	+
	Timmermans 2014	-	?	?	-	-	+	+
	Veirimaa 2015	+	?	+	+	+	+	+
Ultrasonography vs clinical examination	Sjödahl 2011	+	+	+	+	+	+	+
CT-scan vs ultrasonography	Näsvall 2014	+	?	?	+	+	+	+
Imaging vs clinical examination	Donahue 2014	-	+	-	?	+	+	+
	Hansson 2013	-	?	+	-	-	+	+
	Hotouras 2013	-	?	?	-	-	?	?
Peroperative diagnosis	Näsvall 2014	+	+	+	+	+	+	+
	Fleshman 2014	-	-	-	-	-	?	?

High
 Unclear
 Low

Figure 2 Risk of bias and applicability concerns summary

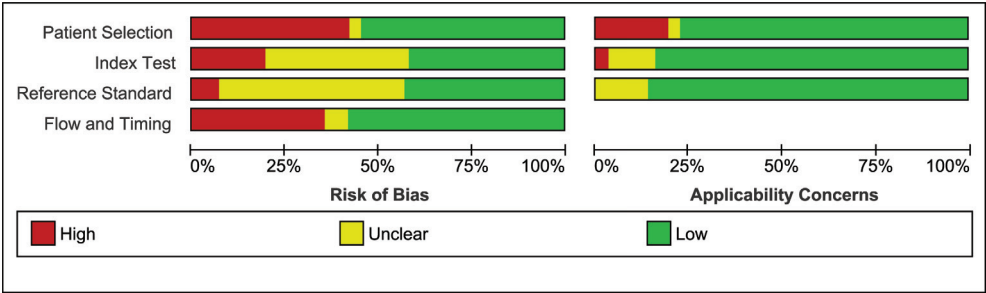


Figure 3 Overall risk of bias and applicability concerns

Supporting information

Supplemental Table 1

Statistical level of agreement with Fleiss' Kappa Values	
Kappa value	Statistical level of agreement
<0	Poor
0.01-0.20	Slight agreement
0.21-0.40	Fair agreement
0.41-0.60	Moderate agreement
0.61-0.80	Substantial agreement
0.81-1.00	Almost perfect agreement

Supplemental Table 2 CT versus clinical examination, contingency tables.

Aslam	Risk of bias	++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	18%	CT +	3	0	3
	Incidence CT	18%	CT -	0	14	14
	Relative increase	1.0	Total	3	14	17
Canda	Risk of bias	+	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	22%	CT +	15	4	19
	Incidence CT	28%	CT -	0	48	48
	Relative increase	1.27	Total	15	52	67
Cingi	Risk of bias	+	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	52%	CT +	12	6	18
	Incidence CT	86%	CT -	0	3	3
	Relative increase	1.5	Total	12	9	21
Conde-Muino	Risk of bias	++++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	3%	CT +	1	1	2
	Incidence CT	7%	CT -	0	29	29
	Relative increase	2.0	Total	1	30	31

Etherington	Risk of bias	+++	4 x 4 Table			
	Level of evidence	4		CE +	CE -	Total
	Incidence CE	29%	CT +	8	2	10
	Incidence CT	36%	CT -	0	18	18
	Relative increase	1.25	Total	8	20	28
Hauters	Risk of bias	++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	3%	CT +	1	1	2
	Incidence CT	7%	CT -	0	27	27
	Relative increase	2.0	Total	1	28	29
Hino	Risk of bias	+++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	20%	CT +	16	10	26
	Incidence CT	17%	CT -	12	21	33
	Relative increase	0.93	Total	28	31	59
Hong	Risk of bias	++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	27%	CT +	29	7	36
	Incidence CT	33%	CT -	0	72	72
	Relative increase	1.24	Total	29	79	108
Köhler	Risk of bias	-	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	1%	CT +	1	2	3
	Incidence CT	4%	CT -	0	48	48
	Relative increase	3.0	Total	1	50	51
Lambrecht	Risk of bias	++++	4 x 4 Table			
	Level of evidence	1b		CE +	CE -	Total
	Incidence CE	24%	CT +	10	9	19
	Incidence CT	33%	CT -	4	35	39
	Relative increase	1.36	Total	14	44	58

Moreno-Matias	Risk of bias	++++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	44%	CT +	23	12	35
	Incidence CT	47%	CT -	10	30	40
	Relative increase	1.06	Total	33	42	75
Näsvall 2017	Risk of bias	-	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	22%	CT +	5	2	7
	Incidence CT	15%	CT -	6	34	40
	Relative increase	0.64	Total	11	36	47
Seo	Risk of bias	++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	24%	CT +	20	4	24
	Incidence CT	29%	CT -	0	59	59
	Relative increase	1.2	Total	20	63	83
Serra-Aracil	Risk of bias	+++	4 x 4 Table			
	Level of evidence	1b		CE +	CE -	Total
	Incidence CE	28%	CT +	15	3	18
	Incidence CT	33%	CT -	0	36	36
	Relative increase	1.2	Total	15	39	54
Veirimaa	Risk of bias	+++	4 x 4 Table			
	Level of evidence	1b		CE +	CE -	Total
	Incidence CE	25%	CT +	17	16	33
	Incidence CT	49%	CT -	0	34	34
	Relative increase	1.94	Total	17	50	67
Fleshmana	Risk of bias	-				
	Level of evidence	1b				
	Incidence CE	13%				
	Incidence CT	11%				

Ihnát	Risk of bias	+++	
	Level of evidence	2b	
	Incidence CE	48%	
	Incidence CT	53%	
Nikberg	Risk of bias	-	
	Level of evidence	2b	
	Incidence CE	25%	
	Incidence CT	53%	141 CT of 187 patients
Odensten	Risk of bias	++	
	Level of evidence	1b	
	Incidence CE	29%	
	Incidence CT	35%	198 CT of 211 patients
Timmermans	Risk of bias	-	
	Level of evidence	2b	
	Incidence CE	53%	
	Incidence CT	53%	87 CT of 150 patients

CE, clinical examination; CT, computed tomography scan.

^a CT if there was clinical suspicion that a hernia was present.

Supplemental Table 3 Ultrasonography versus clinical examination, contingency table.

Sjödahl	Risk of bias	++++	4 x 4 Table			
	Level of evidence	2b		CE +	CE -	Total
	Incidence CE	61%	US +	9	6	15
	Incidence US	35%	US -	17	11	28
	Relative increase	0.58	Total	26	17	43 ^a

CE, clinical examination; US, ultrasonography.

^a All patients with peristomal bulging.

Supplemental Table 4 CT versus ultrasonography.

Näsvall 2014	Risk of bias	++
	Level of evidence	2b
	Incidence CT	80%
	Incidence 3D US	75%
	Relative increase	-

CT, computed tomography scan; US, ultrasonography.

Supplemental Table 5 Perioperative diagnosis, contingency tables.

Näsvall 2014	Risk of bias	++++	4 x 4 Table			
	Level of evidence	2b		CT +	CT -	Total
	Incidence CT	80%	Surgery +	15	3	18
	Incidence surgery	90%	Surgery -	1	1	2
			Total	16	4	20
Näsvall 2014	Risk of bias	++++	4 x 4 Table			
	Level of evidence	2b		3D US +	3D US -	Total
	Incidence 3D US	75%	Surgery +	15	3	18
	Incidence surgery	90%	Surgery -	0	2	2
			Total	15	5	20
Fleshman	Risk of bias	-				
	Level of evidence	1b				
	Incidence CE	13%				
	Incidence CT	11%				
	Incidence surgery	13%				

CT, computed tomography scan; US, ultrasonography.

Supplemental Table 6 Imaging versus clinical examination, contingency tables.

Donahuea	Risk of bias	+	4 x 4 Table			
	Level of evidence	2b		CE +	CE-	Total
	Incidence CE	24%	Imaging +	93	44	137
	Incidence imaging	36%	Imaging -	0	249	249
	Relative increase	1.47	Total	93	293	386
Hansson	Risk of bias	+				
	Level of evidence	2b				
	Incidence CE	5%				
	Incidence imaging	7%	Imaging: CT or MRI when in doubt			
			27 patients had a CT or MRI			

CE, clinical examination; CT, computed tomography scan; MRI, magnetic resonance imaging.

^a Imaging = CT or MRI.

Appendix 1 Literature search syntax.

Embase.com

('parastomal hernia'/exp OR ((stoma/exp OR 'enterostomy'/exp) AND ('abdominal wall hernia'/de OR hernia/de OR hernioplasty/de OR 'herniorrhaphy'/de)) OR (((parastoma* OR stoma OR stomal OR colostom* OR ileostom* OR jejunostom* OR parajejunostom* OR cecostom* OR paracecostom* OR duodenostom* OR paraduodenostom* OR urostom* OR paracolostom* OR paraileostom* OR paraurostom*) NEAR/6 (hernia* OR hernioplast* OR herniorrha*)))ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline Ovid

((exp Surgical Stomas/ OR exp Enterostomy/) AND (Hernia, Ventral/ OR Hernia, Abdominal/ OR Hernia/ OR Herniorrhaphy/)) OR (((parastoma* OR stoma OR stomal OR colostom* OR ileostom* OR jejunostom* OR parajejunostom* OR cecostom* OR paracecostom* OR duodenostom* OR paraduodenostom* OR urostom* OR paracolostom* OR paraileostom* OR paraurostom*) ADJ6 (hernia* OR hernioplast* OR herniorrha*)))ab,ti.) NOT (letter OR news OR comment OR editorial OR congresses OR abstracts).pt. AND english.la.

Cochrane CENTRAL

(((((parastoma* OR stoma OR stomal OR colostom* OR ileostom* OR jejunostom* OR parajejunostom* OR cecostom* OR paracecostom* OR duodenostom* OR paraduodenostom* OR urostom* OR paracolostom* OR paraileostom* OR paraurostom*) NEAR/6 (hernia* OR hernioplast* OR herniorrha*)))ab,ti)

Web of Science

TS=((((parastoma* OR stoma OR stomal OR colostom* OR ileostom* OR jejunostom* OR parajejunostom* OR cecostom* OR paracecostom* OR duodenostom* OR paraduodenostom* OR urostom* OR paracolostom* OR paraileostom* OR paraurostom*) NEAR/5 (hernia* OR hernioplast* OR herniorrha*)))) AND LA=(english) AND DT=(article)

Google scholar

"parastomal|stomal|stoma|colostomal|ileostomal|jejunostomal|parajejunostomal|cecostomal|paracecostomal|duodenostomal|paraduodenostomal|urostomal|paracolostomal|paraileostomal|paraurostomal hernia"

Appendix 2 Methodological concerns.

Inter-observer variation

Gurmu	Selection of patients depending on different hospitals (selection bias); No definition used for clinical examination (reporting bias)
Jänes	No major methodological concerns
Strigård	One experienced physicians and two with short training

CT-scan vs. clinical examination

Brandsma	Only a CT-scan was performed when there was a clinical suspicion of a PSH (selection bias)
Canda	Patients with no postoperative available CT-scan were excluded (selection bias); No definition used for clinical examination (reporting bias)
Cingi	Unclear whether comparison was blinded (reporting bias)
Conde-Muino	No major methodological concerns
Etherington	No definition used for imaging (reporting bias)
Fleshman	Only a CT-scan was performed when there was a clinical suspicion of a PSH (selection bias); no definition used (reporting bias)
Hauters	No definition used for clinical examination (reporting bias)
Hino	Unclear whether comparison was blinded (reporting bias)
Hong	Unclear whether comparison was blinded (reporting bias); no definition used for clinical examination (reporting bias)
Köhler	Not all included patients underwent a CT-scan (selection bias); No definition used for clinical examination (reporting bias)
Lambrecht	No major methodological concerns
Moreno-Matias	No major methodological concerns
Näsvall 2017	Part of included patient did not underwent imaging (selection bias); Unclear whether comparison was blinded (reporting bias)
Nikberg	Part of included patient did not underwent imaging (selection bias); Unclear whether comparison was blinded (reporting bias)
Odensten	Part of included patient did not underwent imaging (selection bias)
Seo	Interval between CT-scan and clinical examination unclear
Serra-Aracil	No definition used for clinical examination (reporting bias)
Timmermans	Part of included patient did not underwent imaging (selection bias); Interval between CT-scan and clinical examination unclear
Veirimaa	Unclear whether comparison was blinded (reporting bias)

Ultrasonography vs. clinical examination

Sjödahl	No major methodological concerns
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CT-scan vs. ultrasonography

Näsvall 2014	No definition used (reporting bias)
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Imaging vs. clinical examination

Donahue	No definition used for clinical examination (reporting bias); Unclear whether all patients underwent clinical examination (reporting bias)
Hansson	Only in clinical unconvincing cases a CT-scan or a MRI was performed (selection bias); in one of the participating center a CT-scan or MRI was performed routinely (selection bias)
Hotouras	Patients with no postoperative available CT-scan were excluded (selection bias); only symptomatic or asymptomatic PSHs were reported. No clinical examination was reported (reporting bias)

Peroperative diagnosis

Fleshman	No definition used (reporting bias)
Näsvall 2014	No major methodological concerns

Appendix 3 Definitions of parastomal hernia.

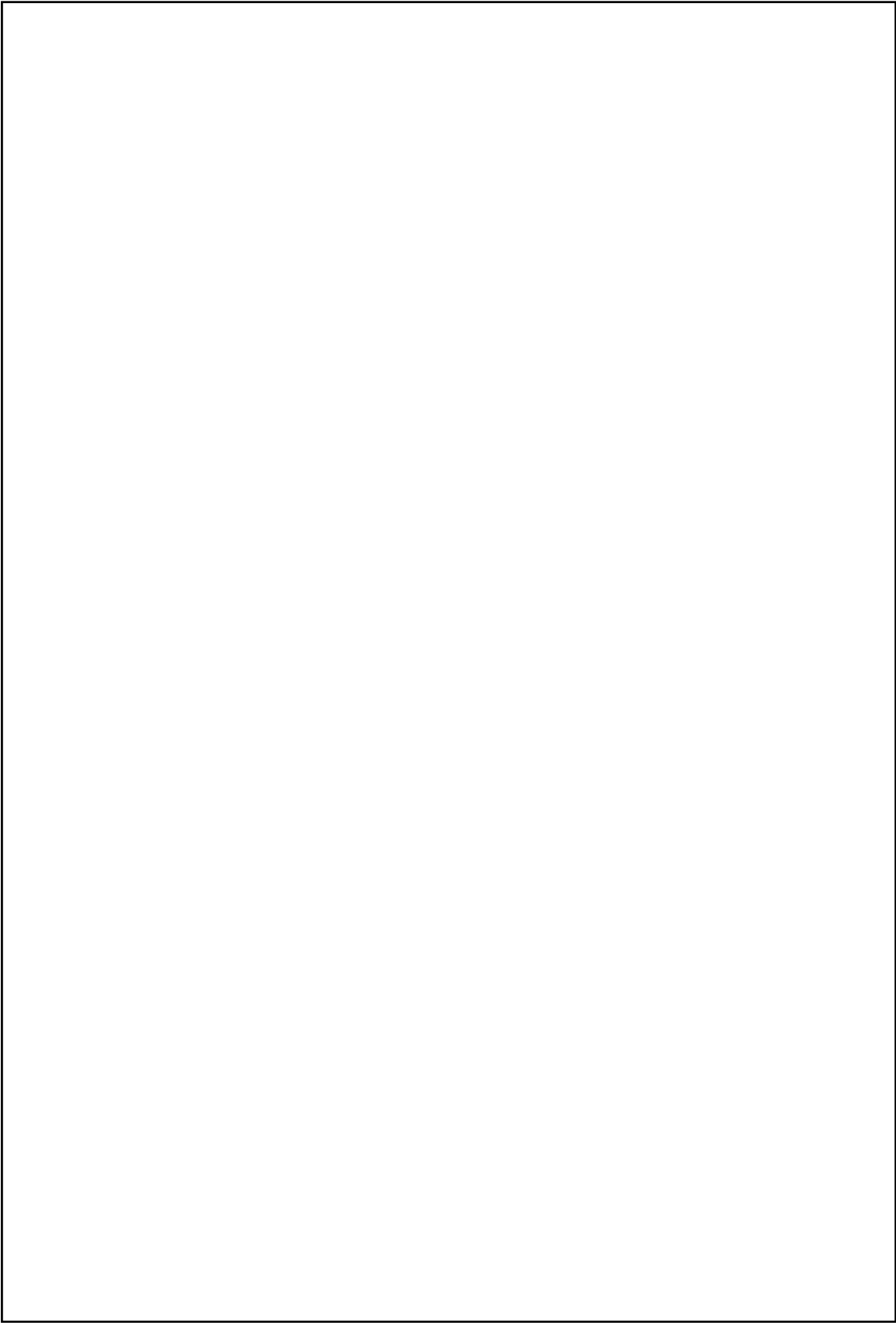
Study	Definition of parastomal hernia
Strigård	‘Defect of the fascia with a protruding hernia sac at the passage of the stoma intestine through the abdominal wall’
Veirimaa	‘Clinically significant parastomal hernia was defined here as parastomal hernia associated with stoma appliance dysfunction and leakage not responsive to conservative measures, peristomal skin breakdown related to sheer injury or ischemia from pressure on the thinned peristomal skin, and recurrent partial bowel obstruction’
Definition clinical examination	
Cingi	‘Bulging during the Valsalva maneuver and palpation of the fascial defect’
Conde-Muino	‘Any noticeable bulge, in the vicinity of the ostomy with the patient erect, supine, and performing the Valsalva maneuver’
Hansson	‘Recurrent or persistent bulge when the patient is standing during a Valsalva maneuver, or palpation of the fascial defect with the patient in the supine position’
Hino	‘Any protrusion around the stoma observed during physical examination’
Jänes	‘Any protrusion in the vicinity of the stoma with the patient straining in a supine and an erect position’
Lambrecht	‘Bulge associated with the stoma’
Seo	‘Any protrusion in the vicinity of the stoma’
Sjödahl	‘A wide opening (more than two fingers) presenting as a manifest parastomal hernia with a palpable bowel segment or omentum passing through the abdominal opening together with the stoma bowel’
Timmermans	‘Any palpable defect or bulge adjacent to the stoma when the patient was supine with their elevated legs or erect and coughing or straining’

Definition imaging

Canda, Conde-Muino, Jänes	'Any intraabdominal content protruding beyond the peritoneum or the presence of a hernia sac'
Donahue, Moreno-Matias	'The protrusion of abdominal contents through the abdominal wall defect created by forming the stoma'
Cingi	'A loop of intestine or any abdominal organ, as well as preperitoneal fat, protruding through the defect alongside the ostomy was considered as parastomal hernia'
Gurmu	'A defect in the fascia through which intraabdominal contents such as omentum or bowel could be extruded out'
Hino	'(1) Herniation of a loop of intestine other than the distal colon , (2) sliding and winding of the distal colon, or (3) herniation of any structures such as the omentum and a wider defect of the parastomal abdominal wall fascia'
Hong	'Any intraabdominal content protruding beyond the fascia or the presence of a hernia sac'
Näsvall 2017	'A peritoneal sac protruding through the fascia beside the stoma bowel'
Nikberg	'Any intra-abdominal content protruding beyond the peritoneum or the presence of a hernia sac at least 1 year after operation'

Appendix 4 Classification of parastomal hernia.

Study	Developed by	Description classification
Brandsma, Köhler, Lambrecht, Näsval 2017, Timmermans, Vierimaa	European Hernia Society	Primary
		Recurrence
		Type 1 <5 cm
		Type 2 <5 cm, concomitant incisional hernia
		Type 3 >5 cm
Brandsma, Donahue, Hauters, Köhler, Lambrecht, Moreno- Matias, Odensten, Seo, Serra-Aracil	Moreno-Matias	Type 4 >5 cm, concomitant incisional hernia
		Type 0 Peritoneum follows the wall of the bowel forming the stoma, with no formation of a sac
		Type 1a Bowel forming the colostomy with a sac <5 cm
		Type 1b Bowel forming the colostomy with a sac >5 cm
		Type 2 Sac containing omentum
		Type 3 Intestinal loop other than the bowel forming the stoma



Chapter 12

Incidence, risk factors and prevention of stoma site incisional hernias: a systematic review and meta-analysis

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*Authors contributed equally

Colorectal Disease 20.10 (2018): 0288-0303

Abstract

Aim

Stoma reversal might lead to a stoma site incisional hernia. Recently, prophylactic mesh reinforcement of the stoma site has gained increased attention, supporting the need for accurate data on the incidence of and risk factors for stoma site incisional hernia and to identify high-risk patients. The aim of this study was to assess incidence, risk factors and prevention of stoma site incisional hernias.

Method

Embase, MEDLINE, Web of Science, Cochrane and Google Scholar databases were searched. Studies reporting the incidence of stoma site incisional hernia after stoma reversal were included. Study quality was assessed with the Newcastle–Ottawa Scale and Cochrane risk of bias tool. Data on incidence, risk factors and prophylactic mesh reinforcement were extracted.

Results

Of 1440 articles found, 33 studies comprising 4679 reversals were included. The overall incidence of incisional hernia was 6.5% [range 0%–38%, median follow-up 27.5 (17.54–36) months]. Eleven studies assessed stoma site incisional hernia as the primary end-point, showing an incidence of 17.7% [range 1.7%–36.1%, median follow-up 28 (15.25–51.70) months]. Body mass index, diabetes and surgery for malignant disease were found to be independent risk factors, as derived from eight studies. Two retrospective comparative cohort studies showed significantly lower rates of stoma site incisional hernia with prophylactic mesh reinforcement compared with nonmesh controls [6.4% *vs* 36.1% ($P = 0.001$); 3% *vs* 19% ($P = 0.04$)].

Conclusion

Stoma site incisional hernia should not be underestimated as a long-term problem. Body mass index, diabetes and malignancy seem to be potential risk factors. Currently, limited data are available on the outcomes of prophylactic mesh reinforcement to prevent stoma site incisional hernia.

Introduction

Temporary stomas are frequently constructed to defunction a low colorectal anastomosis and during surgery for acute complicated diverticulitis, inflammatory bowel disease and traumatic intestinal injury (1-8). Subsequent stoma reversal is associated with surgical site infection (SSI), anastomotic leakage, postoperative ileus and development of stoma site or midline incisional hernia (MIH) (9-13). Stoma site incisional hernia (SSIH) can cause pain, disfigurement, incarceration and strangulation (14, 15).

Recent research has shown that prophylactic mesh reinforcement (PMR) in midline laparotomies in high-risk patients significantly decreases the incidence of MIH (16, 17), and PMR at the stoma site during permanent stoma construction has been considered to reduce rates of parastomal hernia (18-21). Considering the largely comparable pathophysiology, PMR during temporary ostomy takedown to prevent SSIH could also be beneficial by potentially obviating complications and re-operations, and has gained increased attention amongst surgeons (17). Accurate data on incidence and risk factors for the development of SSIH are of importance to correctly assess the clinical value of PMR to prevent SSIH, to facilitate selection of high-risk patients and to aid clinical and shared decision-making (22).

Therefore, the aims of this study were to systematically investigate the literature regarding the incidence of SSIH after stoma reversal, to evaluate potential risk factors for SSIH and to assess the effectiveness of PMR in preventing SSIH.

Methods

The protocol of this study was registered in PROSPERO (CRD42016053347). This study was conducted following the MOOSE guidelines and PRISMA statement (23, 24). Furthermore, decisions on the content were based on items proposed by Wille-Jørgensen *et al.* (25).

Study design and participants

Randomized controlled trials (RCTs) and prospective or retrospective cohort or case-control studies providing data on the incidence of SSIH were included. Case reports, reviews, letters, abstracts or comments were excluded. Studies were included if they met the following criteria: (1) patients ≥ 16 years of age, (2) participants underwent stoma reversal via laparotomy, laparoscopy or local surgery, (3) study outcome included data on the occurrence of SSIH and (4) follow-up duration. Studies reporting on $> 10\%$ of patients with abdominal wall trauma; only reporting on duodeno-/gastro-/oesophago- or urostomies; and only including stoma revisions or re-siting were excluded.

Systematic literature search

A systematic search was performed by a biomedical information specialist. On 4 July 2017, the Embase, MEDLINE, Cochrane, Web of Science and Google Scholar databases were searched. Full search syntaxes and results per database are shown in Appendix S1 in

the online Supporting Information. There was no limit on publication date. Identified articles were reviewed independently by two reviewers (GS and DL) after duplicates were removed on title and abstract, followed by full-text review using EndNote X7®. Differences in article selection were discussed and inclusion or exclusion was performed after consensus was reached between reviewers.

Data extraction

Data extraction was performed by two researchers (GS and DL) and checked by a third independent researcher (RB). Discrepancies were discussed amongst all three researchers, and decisions were made when consensus was reached. In case of uncertainties on reported study results, corresponding authors were contacted if possible. Two researchers (GS and DL) independently assessed the quality of included studies by assessing level of evidence (26), Newcastle-Ottawa Scale (NOS) criteria (nonrandomized studies)(27), and risk of bias (RCTs)(28).

Primary and secondary outcomes

The following outcome variables were extracted: study characteristics (author, year, design, level of evidence, risk of bias, NOS, SSIH detection methods), baseline characteristics [number of patients, gender, age, body mass index (BMI), smoking status, chemotherapy, surgical type and approach, indication, follow-up duration], stoma characteristics [numbers constructed and closed, stoma type (loop colostomy (LC) or ileostomy (LI) and end colostomy (EC) or end ileostomy (EI)), time to closure, closure method and surgical site infection (SSI) after closure] and SSIH characteristics (number of SSIH, SSIH per stoma type and SSIH repairs). Median follow-up for reported cumulative SSI and SSIH rates was calculated based on available follow-up data.

Data synthesis

A Mantel-Haenszel random-effects model was used to calculate pooled odds ratios (ORs), while A Mantel-Haenszel random-effects model was used to calculate pooled odds ratios (ORs), while taking between-study variance and within-study variance into account. ORs with 95% CIs were calculated to assess outcome differences after ileostomy or colostomy reversal. Q statistics and I^2 were calculated to evaluate heterogeneity. All analyses were performed with RevMan 5.3 (Cochrane Centre, Denmark), except for the cumulative meta-analysis, which was performed using R (version 3.4.1.).

Results

Search

A PRISMA flow diagram of the full search results is shown in Fig. 1. After fulfilling the search, a total of 2458 articles were identified, of which 1440 remained after removal of duplicates. After screening on title and abstract and full-text reading, 33 articles were included for qualitative and quantitative analyses (3-8, 29-55). Four articles provided data on outcomes after PMR for prevention of SSIH (45, 46, 56, 57), of which two had a nonmesh control group and could therefore be included in quantitative synthesis (45, 46).

Study characteristics

Study characteristics are shown in Table 1. Two articles were RCTs, 7 were prospective, 23 were retrospective cohort studies and 1 study was case-matched. A total of 6594 nonmesh and 77 mesh patients were available. The majority of studies (20/33) did not specify the SSIH detection method. Two studies specifically mentioned the use of clinical examination and 11 reported on imaging [ultrasound (US), CT or MRI].

Stoma characteristics

An overview of stoma characteristics is shown in Table 2. Overall, 5289 stomas were constructed, of which 4679 (88.5%) were closed. In three studies, the type of colostomy or ileostomy was not clearly described and was therefore reported as total number of colostomies or ileostomies. In all other studies, LI was the most investigated stoma type (28/30), followed by LC (8/30), EC (6/30) and EI (5/30).

Hernia rates

Table 3 provides data on the number of closures, SSIH, SSI and SSIH repairs in individual studies for different stoma types. The rate of SSI after stoma closure ranged from 0% to 18.3% [median follow-up 28 (21.08–36) months]. SSIH rates per stoma type are given in Table 4. The total SSIH rate was 6.5%, with a range from 0% to 38.5% [median follow-up 27.5 (17.54–36) months]. Eleven studies assessed SSIH rate as the primary outcome, whereas the other studies recorded SSIH as a secondary outcome. The SSIH rate of all 11 studies with SSIH rate as the primary outcome was 17.7% [172/970; range 1.7%–36.1%, median follow-up 28 (15.25–51.70) months]. Of these studies, nine used imaging to detect hernias, also leading to a 17.7% rate (139/786; range 1.7%–36.1%). From the 22 studies which did not have SSIH as the primary outcome, an overall rate of 3.6% [129/3622; range 0%–38.5%, median follow-up 27 (16.56–36) months] was found. As calculated from 11 studies (11/33) that used imaging to detect hernias, the SSIH rate was 15.3% [173/1134; range 1.2%–36.1%, median follow-up 28 (15.25–51.7) months]. In contrast, an incidence rate of 3.7% for SSIH [128/3458; range 0%–38.5%, median follow-up 27 (16.56–36) months] was derived from all studies (22/31) that did not use or did not mention the use of imaging for detection of SSIH.

Figure 2 shows a forest plot of seven studies from which data could be used to compare SSIH rates after ileostomy and colostomy reversal. No difference in SSIH risk was found (OR 0.82, 95%CI 0.40–1.69, I^2 0%). Publication bias seemed unlikely, because the study distribution was justifiably symmetrical in an additional funnel plot (Fig. 3). In addition, no differences were found in cumulative meta-analysis (cumulative OR 0.87, 95%CI 0.44–1.75), as shown in Figure S2.

SSIH operation rates

SSIH operation data are shown in Table S1. No data on SSIH operations were available for LC and EI. Of all patients undergoing stoma closure, 6.1% (0%–38.4%) needed an operation for SSIH. Of the patients with SSIH, 51.4% (0%–100%) were operated. In the total ileostomy group, these percentages were 5.6% (0%–12.5%) and 56.4% (0%–100%), respectively, as derived from 10 studies.

Risk factors

Eight studies reported on risk factors for development of SSIH (Table S2)(3-5, 30-32, 45, 52). In univariate analysis, Brook *et al.*(5) found a significantly higher BMI in patients who developed SSIH compared with patients without SSIH (mean 28.4 kg/m² *vs* 24.7 kg/m²). Moreover, they found a significantly higher percentage of clinically obese patients (BMI \geq 30 kg/m²) in the SSIH group (42.3% *vs* 15%, $P < 0.001$). From a logistic regression model, an OR of 1.2 was found for BMI. Furthermore, from a nonparametric correlation test of Stage 1 hypertension (\geq 140/90 mmHg), a Spearman's rho of 0.183 was found ($P = 0.01$). In addition, malignant disease was found to be associated with a higher likelihood of hernia in logistic regression analysis (OR 18, $P = 0.009$) and, albeit in univariate analysis, postoperative complication rates were higher in patients with SSIH (27% *vs* 22%, $P < 0.001$).

Liu *et al.*(45) investigated the influence of PMR versus no mesh in ileostomy closures and assessed potential risk factors. From univariate analyses, the following significant factors were found: age > 60 years, malignant disease, diabetes, hypertension, chronic steroid usage and chronic kidney injury. A multivariate analysis was performed and showed malignancy (OR 21.93, 95% CI 1.58–303.95, $P = 0.02$) and diabetes (OR 20.98, 95% CI 3.23–136.31, $P = 0.001$) to be independent risk factors for SSIH.

Bhangu *et al.*(30) found no significant differences in age or gender for patients with SSIH versus no SSIH. Moreover, no difference in MIH between patients with and without SSIH was found (50% *vs* 41%, $P = 0.51$). Age, SSI, stoma type, gender, BMI and time to closure did not significantly increase the risk of SSIH in the study by Cingi *et al.* (31). However, patients with a MIH had an increased risk (OR 4.4) of SSIH.

De Keersmaecker *et al.*(32) assessed a number of potential patient- and surgery-related risk factors but did not find any significant differences in univariate analysis.

Oriel *et al.*(4) showed that myofascial release was performed more often in the SSIH group (18.2% *vs* 2.9%, $P = 0.02$) and more SSIH patients had superficial incisional SSI (27.3% *vs* 5.8%, $P = 0.01$). From univariate analyses, Saha *et al.*(3) found the development of SSIH to be significantly associated with reoperation after LI reversal (3% *vs* 25%, $P < 0.001$) and emergency surgery (4% *vs* 13%, $P = 0.01$).

Lastly, Schreinemacher *et al.*(52) performed a multivariate analysis for risk factors, which only showed that BMI (\geq 30 kg/m² *vs* < 25 kg/m²) was a significant risk factor (OR 5.53, 95% CI 1.72–17.80), whereas a time to closure of < 6 months did not appear as risk factor (OR 2.38, 95% CI 0.96–5.99, $P = 0.06$).

Prophylactic mesh reinforcement

Four studies provided data on PMR outcomes, of which details are given in Table 5. Bhangu *et al.*(56) used biological mesh (StratticeTM) and intraperitoneal onlay mesh (IPOM) placement in a case series of seven patients. During 30-day follow-up, only one adverse event was seen (a SSI with subsequent superficial wound breakdown) while the mesh was still *in situ* (on US).

In the case series by Van Barneveld *et al.* (57), 10 patients received a Parietex Composite Parastomal® mesh during creation of a temporary stoma for parastomal hernia prophylaxis (IPOM placement). At stoma reversal, mesh continuity was restored to serve as SSIH prophylaxis. No serious mesh-related or other serious complications were observed during 12 month' follow-up. After a median follow-up of 26 months [interquartile range (IQR) 14–29], no SSIH was found during physical and US examination in nine patients.

Two other studies, by Liu *et al.* and Maggiori *et al.*, were comparative cohort studies, including 83 and 94 patients, respectively (45, 46). In the retrospective study by Liu *et al.* (45), consecutive patients undergoing ileostomy closure were included, of whom 47 (56.6%) had PMR with polypropylene mesh (Ultrapro, Ethicon Inc.) placed in an onlay position by the same surgeon in all patients. During median follow-up of 18.2 months (IQR 11.7–30.8), three SSIHs (6.4%) were detected in mesh patients, whereas 13 SSIHs (36.1%) were found in control patients (OR 8.29, 95% CI 2.14–32.08, $P = 0.001$). SSIH in the mesh group was small and asymptomatic, and did not require repair, compared with 23% SSIH repairs in control patients. In the matched case–control study by Maggiori *et al.* (46), 30 consecutive patients were individually matched to patients from a prospective database. In these patients, a biological mesh (noncross-linked collagen, porcine dermal matrix; Meccellis BioTech, France) was placed in a retromuscular position. At 1-year CT follow-up, SSIH incidence was lower in mesh patients than the control group (3% *vs* 19%, $P = 0.04$), while postoperative morbidity was similar in both groups (17% *vs* 11%, $P = 0.51$). SSIH repair was needed in eight control patients (13% *vs* 0%, $P = 0.05$).

Discussion

This study shows an overall incidence of SSIH of 6.5% [range 0%–38.5%, median follow-up 27.5 (17.54–36) months], which is in accordance with the review by Bhangu *et al.* (58), who reported an overall hernia rate of 7% (range 0%–48%, median follow-up 36 months). However, this study was based on a smaller number of patients ($n = 2698$) than the present study ($n = 4602$). Both previous studies, by Bhangu *et al.* and Nguyen *et al.*, reported on significant heterogeneity between studies and difficulties in interpretation and combining study results (58, 59). To reduce this heterogeneity, several inclusion and exclusion criteria were used during our systematic literature search (Fig. 1). Most importantly, to be included, studies had to mention follow-up duration, since hernia rates increase over time and might vary between different durations. Furthermore, studies with > 10% of patients with abdominal trauma were excluded, as earlier reports showed these patients to be more prone to hernia development (60, 61).

To compare the SSIH rate between ileostomy and colostomy reversal, seven studies were eligible for analysis. Whereas the previous review of Bhangu *et al.* (58) showed a significantly different lower SSIH rate after ileostomy (OR 0.28, 95% CI 0.12–0.65), this review found no significant difference in the risk of SSIH between ileostomy and

colostomy (OR 0.82, 95% CI 0.40–1.69), which was also not found in an additional cumulative meta-analysis (cumulative OR 0.87, 95% CI 0.44–1.75).

In this study, only one-third (11/33) of included studies assessed SSIH incidence as the primary outcome. Twenty studies did not mention detection methods and, therefore, it seems likely to assume that imaging was not used in these studies. To investigate potential underestimation, the overall incidence of SSIH from the 11 studies with SSIH as the primary outcome was calculated (17.7%, range 1.7%–36.1%) (4, 5, 30–32, 37, 45, 46, 48, 51, 52). These rates indeed support the hypothesis that the overall incidence of hernia from all included studies (6.5%), as from those only reporting on SSIH as a secondary outcome (3.6%), is an underestimation. The potential risk of underestimation by not using imaging for detection of SSIH is further supported by the higher incidence in studies that used imaging, compared with studies that did not use, or did not mention the use of imaging as a detection method (15.3% *vs* 3.7%, respectively). Indeed, from the literature on incisional hernias it is known that prevalence rates vary substantially, through differences in diagnostic modalities, observer, definition and diagnostic protocol (62). The use of imaging, which led to higher SSIH rates, might have identified asymptomatic or occult hernias. Therefore, the overall SSIH rate of 6.5% seems to be lower but more clinically relevant, and thus it remains debatable if PMR might even be necessary at all. Hence, it is important to identify high-risk patients, in whom PMR might still be of added value and if in these patients its risks outweigh its benefits.

Eight studies were identified that reported on potential risk factors for development of SSIH. Three studies (5, 45, 52) performed a multivariate analysis, from which BMI, primary surgery for malignant disease and diabetes mellitus were identified as potential risk factors. BMI is known to affect midline incisional and parastomal hernia rates (16, 63–66), which might be explained by higher intra-abdominal pressure and consequent higher abdominal wall tension (16, 67). Additionally, obesity and diabetes are associated with wound healing complications due to local hypoxia, caused by a decreased vascularization of adipose tissue and other microvascular changes, impairing collagen synthesis and having a negative effect on the overall healing process (16, 68). Smoking has a comparable negative effect on wound healing and is considered a risk factor for incisional hernia (69). However, none of the included studies has shown a significant effect on occurrence of SSIH. Moreover, with regard to primary surgery for malignant disease, factors as malnutrition, poor general health and immunosuppressive effects of chemotherapy are thought to negatively affect the normal healing process (45, 68, 70). Wound infections are known to increase the risk of hernia formation (63, 71), however, in the present literature review SSIs were not found to be independently associated with an increased risk of SSIH. Overall, the study by Oriel *et al.* (4) was the only study to identify superficial SSI as a factor contributing to future SSIH formation. The data on risk factors in this review might help with the selection of high-risk patients and therefore help guide clinical decision-making, potentially involving PMR. Moreover, since factors such as obesity and smoking can potentially be minimized, it might be of interest to focus not only on PMR but also on lifestyle interventions such as preoperative weight loss, smoking cessation and nutritional optimization for the prevention of SSIHs.

However, to date no evidence is available on the efficacy or effectiveness of these lifestyle interventions with regard to incidence of SSIH.

Four studies reported on PMR for SSIH prevention (45, 46, 56, 57). These studies had several methodological limitations that made it difficult to draw conclusions about the potential added value of PMR. Two of the studies reported on a very limited number of patients ($n < 10$), decreasing their generalizability (56, 57). Furthermore, these studies had no control (nonmesh) group. Two other studies on PMR were of better quality because they included larger numbers of patients and as well as control patients (45, 46). Liu *et al.* (45) stated that mesh placement significantly reduced the incidence of SSIH following ileostomy closure, without an increase in complications. Maggiori *et al.* (46) reported a significant difference in SSIH on 1-year follow-up CT in favour of PMR. Nevertheless, all four studies recognized the need for RCTs to further evaluate the beneficial effects, safety and (cost-) effectiveness of PMR. Efforts have already been made by several research groups, and further trial results are awaited. A feasibility study by the Reinforcement of Closure of Stoma Site (ROCSS) Collaborative has recently been published and reported their study protocol to be feasible, without early safety concerns (72). Based on their data, progression towards their ROCCS trial (ClinicalTrials.gov identifier NCT02238964) has continued (72, 73). Several other trials have been initiated, such as the MEMBO trial (NCT02576184), the ILEOCLOSE trial (NCT02226887) and the LISTO-trial (NCT02669992). Next to ileostomy closure, only the ROCCS trial also includes patients undergoing colostomy closure, and none of these trials focuses on a specific risk group, such as obese patients. However, since obesity seems to increase the risk of SSIH after stoma closure, this group of patients might potentially benefit more from PMR, although, paradoxically, these patients, especially in case of diabetes, might at the same time also be at higher risk of developing mesh-related complications (74, 75). Therefore, it would be interesting to see the results of PMR in these patients specifically. With regard to the efficacy and (cost-)effectiveness of PMR, it is still debatable as to what would be a clinically significant reduction in SSIH rates. In the case of the ROCCS trial, sample size calculation of the full Phase III study was based on a 40% reduction (25% to 15%) in the 2-year clinical hernia rate (72). In the study by Maggiori *et al.* (46), a 16% difference was found (19% vs 3%, $P = 0.043$), which might have been used for the sample size calculation of the MEMBO trial. However, further data on sample size calculations and risk reduction were not available. Unfortunately, robust conclusions cannot yet be drawn on its risks and benefits from the available literature on PMR. If PMR is proven to be beneficial in these studies, further implications for practice should be made sufficiently clear (e.g. patient selection) in order to overcome the barriers of implementing these findings (76).

The low level of evidence and the vast heterogeneity of the included studies are two important limitations of this study. Nevertheless, inclusion of these studies was still deemed necessary as they allowed a more comprehensive overview of potential risk factors, as well as more detailed analyses of SSIH and repair rates. The lack of a predefined time period from which studies could be included might also have been a limitation of this review, because important changes in operative and perioperative care of patients have been introduced in recent decades (e.g. laparoscopy). However, this effect is presumably

largely negligible since the majority of included studies were published in the previous decade (Table 1).

In conclusion, this review shows an overall incidence of SSIH of 6.5% (range 0%–38.5%), as well as an incidence of 17.7% (range 1.7%–36.1%) from 11 studies assessing SSIH as the primary outcome. Furthermore, potential risk factors have been identified, of which BMI, malignant disease and diabetes were considered to be the most important. Lastly, early results from four studies on PMR were identified, but no robust conclusions could be drawn. Results of ongoing trials are awaited.

Acknowledgements

The authors thank Wichor Bramer, biomedical information specialist at the Erasmus Medical Center, for his assistance with the search strategy and syntax.

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Table 1 Study characteristics

Author	Year	Study details		Patients		Male (%)	Age (years)	BMI (kg/m ²)	Smoking (%)	Follow-up details		Method of closure	Method of SSIH detection
		Design	LOE	NOS	Number					Chemo (%)	Total duration		
Bakx	2004	R	2b	6	69	53.6	57 (28-83)	-	-	-	24w (2-124)	-	-
Bhangu	2012	R	2b	6	59	76	62.7 (13.4)	-	-	-	-	-	C, CT or MRI
Brook	2016	R	2b	8	193	59.6	66 (20-92)	25 (16-44)	16	18.7	6m (0.36)	20.5m (0-69)	C, US, CT
Cingi	2008	P	2b	6	31	48.4	Hernia: 60.9 (11.0) No hernia: 68 (14.3)	Hernia: 30.1 (6.2) No hernia: 26.2 (4.9)	-	-	26m (3-118)	-	C, US
De Keersmaecker	2016	R	2b	6	153	60.1	67.1 (11.6)	-	-	-	66d (25-356)	2.56y (1.62)	CT
D'Haenck	2011	R	2b	6	197	54.8	56.2 (15.4)	23.8 (3.8)	-	-	34m (1.9-64.2)	-	Primary
Edwards	2001	RCT*	1b	-	LC: 36 LI: 34	LC: 79.4 LI: 61.1	LC: 68 (32-90) LI: 63 (40-85)	-	-	-	LC: 73d (28-141) LI: 62d (17-120)	36m (6-48)	Primary
El-Hussuna	2012	R	2b	5	159	67.3	65 (39-88)	24 (16.4-35.9)	17.6	-	95w (1-242)	-	Primary
Fiscun	2014	P	2b	6	20	75	65.4 (53.1-72.1)	25.8 (23.9-28)	-	-	44.1m (23.5-58.8)	-	Primary
Garcia-Borello	2004	R	2b	6	127	57.5	54 (18-58)	-	-	-	9.1m (18.6)	18.9m (5.2)	Primary
Giannakopoulos	2009	R	2b	5	119	57.1	55 (39-66)	24.4 (22.3-26.8)	-	-	106d (69-174)	>2m	Primary
Guzman-Valdivia	2008	R	2b	6	70	59	61 (36-87)	36 (25-52)	-	-	-	28m (2-87)	Primary
Hasegawa	2000	RCT*	1b	-	27	7.7	45.7 (23-76)	-	-	-	4m	-	Primary
Holmgren	2017	R	2b	8	316	56.7	67 (37-86)	-	-	-	272d (55-1142)	-	-
Köhler	2014	R	2b	6	14	57.1	66 (43-86)	26.7 (20.4-31.8)	-	64.2	26m (18-36)	-	Primary
Krand	2008	P	2b	7	50	68	61 (23-78)	-	-	-	A: 12w (7-33) B: 12d (10-14)	A: 27m (4-50) B: 24m (3-49)	Primary

Author	Year	Study details		Patients		Follow-up details					Method of closure	Method of SSIH detection			
		Design	LOE	NOS	Number	Male (%)	Age (years)	BMI (kg/m ²)	Smoking (%)	Chemo (%)			Total duration	Time to closure	Time since closure
Lewis Li	1990	P	2b	6	50	65	35 (17-71)	-	-	-	-	9w (5-53)	0.5-2y	Primary	-
	2017	R	2b	9	SSE: 139 NSSE: 599	SSE: 43.2 SSE: 57.8	SSE: 40.7 (13.4) NSSE: 42.8 (15.9)	SSE: 25.5 (5.6) NSSE: 25.9 (5.9)	-	2.7	SSE: 23.2m (14.7-36.2) NSSE: 32.7m (18.5-48.6)	SSE: 4.7m (3.0-9.0) NSSE: 5.4 (3.1-7.4)	SSE: 16.4m (7.7-30.6) NSSE: 25.6m (12.3-41.8)	-	-
Liang	2013	R	2b	6	No SSI: 82	No SSI: 94	No SSI: 64 (9.3)	No SSI: 27 (6.3)	-	-	No SSI: 32m (1-71)	No SSI: 10m (7.0)	-	No SSI: 49 open; 20 closed; 13 loose	C, CT
Liu	2013	R	2b	9	Mesh: 47	Mesh: 63.8	Mesh: 69.6 (57.9-76.0)	Mesh: 9 patients >30	-	Mesh: 51.1	18.2m (11.7-30.8)	Mesh: 9.2m (4.1-15.0)	-	Mesh: onlay; skin defect open	C, CT
Luglio Maggiori	2011	P	2b	5	944	56.9	47.2 (16.8)	25.7 (5.2)	-	-	-	-	30d	-	-
	2015	CM	3b	9	Mesh: 30	Mesh: 60	Mesh: 61 (13, 25-79)	Mesh: 26 (4, 19-36)	-	-	Mesh: 16.8m (3.3, 11.4-23.9)	Mesh: 11w (5, 5-26)	Mesh: 16.8m (3.3, 11.4-23.9)	Mesh: sublay; primary	CT
Mala Mishra	2008	R	2b	6	72	56	65 (39-89)	-	-	-	-	-	36m (2-118)	-	-
	2014	R	2b	6	Lap: 289	Lap: 50.2 (23.3)	Lap: 68.2 (23.3)	-	-	-	44m (9-72)	9m (3-33)	-	-	C, CT
Oriol	2017	R	2b	6	114	Hernia: 100	Open: 68.5 (38.8)	Hernia: 29.9 (5.9)	Hernia: 54.6	-	5.7y (0.5-14)	Hernia: 245.1d (218.5)	5.7y (0.5-14)	-	-

Author	Year	Study details		Patients		Follow-up details							Method of closure	Method of SSIH detection	
		Design	LOE	NOS	Number	Male (%)	Age (years)	BMI (kg/m ²)	Smoking (%)	Chemo (%)	Total duration	Time to closure			Time since closure
Rosen	2005	R	2b	6	22	45.5	54 (33-73)	26 (19-34)	~	~	14.7m	168d (69-385)	14.7m	~	~
Rutegard	1987	R	2b	6	56	LC: 57.1 94	LC: 72 (38-94)	~	~	~	36-60m	~	~	~	~
Saeed	2012	P	2b	6	179	LI: 51.6 71.2	LI: 67 (26-89) 66 (29-79)	~	~	~	3y	6m (2-22)	1y (n= 43), 2y (n= 28), 3y (n= 12)	~	CT
Saha	2009	R	2b	6	325	53	59 (16-90)	~	~	15.7	67m (12-96)	34w (19-57)	67m (12-96)	~	~
Schreinemacher	2011	P	2b	8	111	50.5	62 (18-84)	<25 (40.5); 25-29.9 (39.6); >30 (19.8)	~	~	35m (5-77)	6m (1-48)	35m (5-77)	Primary = 99 Secondary = 12	C, US
Seo	2013	R	2b	6	836	66.7	56 (11)	~	~	~	54m (6-146)	7m (3)	~	~	C, US, CT
Vermeulen	2009	R	2b	6	HP: 139	HP: 55.6	HP: 61 (23-85)	~	~	~	18-150m	~	~	~	C
Welten	1991	R	2b	6	PA: 19 30	PA: 84 63.3	PA: 63 (38-82) 64.6 (56-84)	~	~	~	25m (6-52)	3.5m (1-7)	~	~	~

Continuous data are median (interquartile range), mean (standard deviation) or mean (standard deviation, range). A, delayed closure group; B, early closure group; BMI, body mass index; C, clinical diagnosis; CM, case matched; CT, computed tomography diagnosis; d, days; HP, Hartmann's procedure; Lap, laparoscopic; LI, loop ileostomy; LC, loop colostomy; LOE, level of evidence; m, months; MRI, magnetic resonance imaging; NOS, Newcastle-Ottawa scale; NSSF, nonstoma site extraction; P, prospective; PA, primary anastomosis with diverting ileostomy; R, retrospective; RCT, randomized controlled trial; SSI, surgical site infection; SSIH, stoma site incisional hernia; SSF, stoma site extraction; US, ultrasound; y, years. *Data on risk of bias are given in Figure S1.

Table 2 Stoma characteristics

Author	Year	Stomas formed	Stomas closed	Indications for stoma formation				Primary surgery				Stoma types						
				CRC	DIV	IBD	Trauma	Other	Acute	Elective	Lap	Open	LC	LI	EC	EI	C (total)	I (total)
Bakx	2004	69	60	36	12	12	0	9	-	-	-	-	0	69	0	0	0	69
	2012	59	59	-	-	-	-	-	-	-	-	-	0	49	10	0	10	49
	2016	193	193	102	20	47	0	24	23	169	50	139	0	193	0	0	0	193
	2008	31	31	23	4	-	-	-	-	-	0	31	8	4	16	3	24	7
	2016	153	153	153	0	0	0	0	0	0	153	53	100	0	153	0	0	153
D'Haeninck	2011	197	197	138	0	41	0	18	-	-	-	-	0	197	0	0	0	197
Edwards	2001	70	63	70	0	0	0	0	-	70	-	-	36	34	0	0	36	34
El-Hussuna	2012	159	158	159	0	0	0	0	0	159	0	159	0	158	0	0	0	158
Fiscun	2014	20	20	3	12	0	0	5	-	-	3	17	0	0	20	0	20	0
Garcia-Borello	2004	127	109	72	5	32	1	17	-	118	-	-	0	127	0	0	0	127
Giannakopoulos	2009	119	119	49	10	33	2	25	-	-	-	23	0	119	0	0	0	119
Guzman-Valdivia	2008	70	70	12	43	0	3	12	-	-	-	-	-	-	-	-	65	5
Hasegawa	2000	13	13	0	0	0	0	13	-	-	-	-	12	1	0	0	12	1
Holmgren	2017	273	229	273	0	0	0	0	-	-	-	-	38	235	0	0	38	235
Köhler	2014	14	14	10	4	0	0	0	-	-	4	10	0	14	0	0	0	14
Krand	2008	50	50	46	0	2	0	2	0	50	-	-	0	50	0	0	0	50
Lewis	1990	50	40	0	0	50	0	0	0	50	-	-	0	50	0	0	0	50
Li	2017	SSE: 139 NSSE: 599	SSE: 139 NSSE: 597	SSE: 23 NSSE: 119	0	SSE: 106 NSSE: 449	0	SSE: 10 NSSE: 31	-	-	-	-	0	SSE: 51 NSSE: 286	0	SSE: 88 NSSE: 313	0	SSE: 139 NSSE: 599
Liang	2013	no SSL: 82	no SSL: 63	-	-	-	-	-	no SSL: 45	no SSL: 37	no SSL: 19	no SSL: 63	no SSL: 7	no SSL: 41 SSE: 18	no SSL: 18	no SSL: 16	no SSL: 25	no SSL: 57
Liu	2013	SSE: 46 Mesh: 47 Control: 36	SSE: 40 Mesh: 47 Control: 36	63	6	9	0	5	SSE: 34	SSE: 12	SSE: 16	SSE: 30	SSE: 5	SSE: 13	SSE: 21	SSE: 7	SSE: 26	SSE: 20
Luglio	2011	944	944	279	64	507	0	94	-	944	-	-	0	944	0	0	0	944
Maggiori	2015	Mesh: 30 Control: 64	Mesh: 30 Control: 64	Mesh: 30 Control: 64	0	0	0	0	0	Mesh: 30 Control: 64	Mesh: 30 Control: 64	0	0	Mesh: 30 Control: 64	0	0	0	Mesh: 30 Control: 64

Author	Year	Stomas formed	Stomas closed	Indications for stoma formation				Primary surgery			Stoma types					C (total)	I (total)
				CRC	DIV	IBD	Trauma	Other	Acute	Elective	Lap	Open	LC	LI	EC	EI	
Mala	2008	72	62	72	0	0	0	0	-	-	-	-	10	61	0	1	10
Mishra	2014	Lap: 35 Open: 282	Lap: 12 Open: 68	Lap: 35 Open: 282	0	0	0	0	-	-	289	768	-	-	-	-	Lap: 16 Open: 135
Oriel	2017	114	114	Hernia: 2	Hernia: 6	Hernia: 0	0	Hernia: 3	Hernia: 0	Hernia: 11	-	-	-	-	-	-	Hernia: 6 5
Rosen	2005	22	22	2	15	0	1	4	-	-	20	2	0	0	22	0	22
Rutegard	1987	61	23	19	15	3	0	19	40	21	-	-	29	32	0	0	29
Saeed	2012	179	59	-	-	-	-	-	-	-	-	-	0	92	0	87	0
Sah	2009	325	325	160	25	118	0	22	55	270	-	-	0	325	0	0	325
Schreinemacher	2011	111	111	53	0	33	0	25	-	-	-	-	64	47	0	0	64
Seo	2013	246	245	246	0	0	0	0	0	836	-	-	0	246	0	0	246
Vermeulen	2009	HP: 139	HP: 63	0	HP: 139	0	0	0	HP: 139	0	-	-	0	19	139	0	139
Wälten	1991	30	23	-	-	-	-	-	24	6	-	-	0	30	0	0	30

C, colostomy; CRC, colorectal carcinoma; DIV, diverticular disease; EC, end colostomy; EI, end ileostomy; IBD, inflammatory bowel disease; Lap, laparoscopic; LC, loop colostomy; LI, loop ileostomy; NSSE, nonstoma site extraction; PA, primary anastomosis with diverting ileostomy; SSI, surgical site infection; SSE, stoma site extraction.

Table 3 Hernia rates (subdivided per study)

Author	Year	All stomas	SSIH per stoma type												SSIH repair		
			Number of stomas closures	Number of SSIH (%)	Number of SSI (%)	LC		LI		EC		EI		C (total)		I (total)	
						Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)	Closed			SSIH (%)
Bakx	2004	60	5 (8.3)	4 (6.7)	0	0	60	5 (8.3)	0	0	0	0	0	0	60	5 (8.3)	-
Bhangu	2012	59	20 (33.9)	-	0	0	49	16 (32.7)	10	4 (40)	0	0	10	4 (40)	49	16 (32.7)	4
Brook	2016	193	26 (13.8)	-	0	0	193	26 (13.8)	0	0	0	0	0	0	193	26 (13.8)	19
Cingi	2008	31	10 (32.3)	4 (12.9)	8	3 (37.5)	4	2 (50)	16	5 (31.3)	3	0	24	8 (33.3)	7	2 (28.6)	3
De Keersmaecker	2016	153	17 (11.1)	-	0	0	153	17 (11.1)	0	0	0	0	0	0	153	17 (11.1)	6
D'Haeninck	2011	197	7 (3.6)	9 (4.6)	0	0	197	7 (3.6)	0	0	0	0	0	0	197	7 (3.6)	7
Edwards	2001	63	5 (7.9)	LC: 2 (6.5) LI: 1 (3.1)	31	5 (16.1)	32	0	0	0	0	0	31	5 (16.1)	32	0	-
El-Hussuna	2012	158	8 (5.1)	8 (5.1)	0	0	158	8 (5.1)	0	0	0	0	0	0	158	8 (5.1)	-
Fiscun	2014	20	3 (15)	0	0	0	0	0	20	3 (15)	0	0	20	3 (15)	0	0	3
Garcia-Botello	2004	109	13 (11.9)	20 (18.3)	0	0	109	13 (11.9)	0	0	0	0	0	0	109	13 (11.9)	8
Giannakopoulos	2009	119	2 (1.7)	12 (10.1)	0	0	119	2 (1.7)	0	0	0	0	0	0	119	2 (1.7)	-
Guzman-Valdivia	2008	70	22 (31.4)	3 (4.3)	-	-	-	-	-	-	-	-	65	21 (32.3)	5	1 (20)	-
Hasegawa	2000	13	5 (38.5)	1 (7.6)	12	-	1	-	0	0	0	0	12	-	1	-	5
Holmgren	2017	229	1 (0.4)	-	34	-	195	-	0	0	0	0	34	-	195	-	-
Köhler	2014	14	4 (28.6)	0	0	0	14	4 (28.6)	0	0	0	0	0	0	14	4 (28.6)	-
Krand	2008	50	1 (2)	4 (8)	0	0	50	1 (2)	0	0	0	0	0	0	50	1 (2)	0
Lewis	1990	40	0	1 (2.5)	0	0	40	0	0	0	0	0	0	0	40	0	0
Li	2017	SSE: 139 NSSE: 597	SSE: 2 (1.4) NSSE: 11 (1.8)	SSE: 4 (2.8) NSSE: 20 (3.4)	0	0	SSE: 51 NSSE: 286	-	0	0	SSE: 88 NSSE: 313	-	0	0	SSE: 139 NSSE: 597	SSE: 2 (1.4) NSSE: 11 (1.8)	-
Liang	2013	no SSI: 63*	no SSI: 15 (23.8)	46	no SSI: 7	-	no SSI: 41	-	no SSI: 18	no SSI: 21	no SSI: 16	-	no SSI: 25	-	no SSI: 57	-	-
Liu	2013	SSI: 40* Mesh: 47	SSI: 16 (40) Mesh: 3 (6.4)	Mesh: 2 (4.3)	0	0	SSI: 13 Mesh: 47	Mesh: 3 (6.4)	0	0	SSI: 7	0	0	0	SSI: 20 Mesh: 47	Mesh: 3 (6.4)	Mesh: 0
Luglio	2011	944	1 (0.1)	44 (4.7)	0	0	944	1 (0.1)	0	0	0	0	0	0	944	1 (0.1)	-
Maggiori	2015	Mesh: 30	Mesh: 1 (3.3)	Mesh: 2 (6.7)	0	0	Mesh: 30	Mesh: 1 (3.3)	0	0	0	0	0	0	Mesh: 30	Mesh: 1 (3.3)	Mesh: 0
		Control: 64	Control: 12 (18.8)	Control: 1 (1.6)	Control: 1	Control: 1	Control: 64	Control: 12 (18.8)	Control: 64	Control: 12 (18.8)	Control: 64	Control: 12 (18.8)	Control: 64	Control: 12 (18.8)	Control: 64	Control: 12 (18.8)	Control: 8

Author	Year	All stomas Number of stoma closures	SSIH per stoma type												SSIH repair	
			Number of SSI (%)		LC		LI		EC		EI		C (total)			I (total)
			Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)	Closed	SSIH (%)		
Mala Mishra	2008	62		5 (8.1)	2 (3.2)	-	-	-	-	-	-	-	-	-	4	3
	2014	Lap: 12 Open: 68	-	Lap: 1 (8.3) Open: 3 (4.4)	-	-	-	-	-	-	-	-	-	-	Lap: 12 Open: 68	1 3
Oriol Rosen	2017	114		11 (9.7)	-	-	-	-	-	-	-	-	-	52	5 (9.6)	6 (10.7)
	2005	22	0	1 (4.5)	3 (13.6)	0	0	0	22	1 (4.5)	0	0	22	1 (4.5)	0	0
Ruegard Saeed	1987	23	-	1 (4.3)	-	15	1 (6.7)	8	0	0	0	0	0	15	1 (6.7)	8
	2012	59	1 (1.7)	1 (1.7)	-	0	0	92	-	0	0	-	0	0	0	59
Saha Schreinemacher	2009	325	18 (5.5)	24 (7.4)	0	0	0	325	18 (5.5)	0	0	0	0	0	325	18 (5.5)
	2011	111	36 (32.4)	12 (10.8)	64	-	47	-	0	0	0	0	64	-	47	18 (5.5)
Seo Vermeulen	2013	245	3 (1.2)	0	0	0	0	245	3 (1.2)	0	0	0	0	0	245	3 (1.2)
	2009	HP: 63 PA: 14	HP: 7 (11.1) PA: 1 (7.1)	0	0	14	1 (7.1)	63	0	0	0	0	63	0	14	1 (7.1)
Welten	1991	23	1 (4.3)	2 (8.7)	0	0	23	1 (4.3)	0	0	0	0	0	0	23	1 (4.3)

C, colostomy; EC, end colostomy; EI, end ileostomy; HP, Hartmann's procedure; Lap, laparoscopic; LC, loop colostomy; LI, loop ileostomy; NSSE, nonstoma site extraction; PA, primary anastomosis with diverting ileostomy; SSI, surgical site infection; SSIH, stoma site incisional hernia; SSE, stoma site extraction.

*Late outcomes of stoma closures were available in 63 of 92 no SSI patients and 40 out of 46 SSI patients.

Table 4 Hernia rates (subdivided by stoma type)

Stoma group	Studies	Number of stomas closed	Number of SSIH detected	Percentage SSIH detected (%)	Range (%)*	Median follow-up (IQR)†
Loop colostomy	3	54	9	16.7	6.7-37.5	36 (36-36)
Loop ileostomy	21	2837	150	5.3	0-50	23.75 (14.92-43.75)
End colostomy	5	131	13	9.9	0-40	12.35 (10-12.35)
End ileostomy	1	3	0	0	-	-
Colostomy	9	302	48	15.9	0-40	28 (12.35-52.20)
Ileostomy	26	3776	175	4.6	0-36.1	27 (18.53-51.50)
Total	33	4602	301	6.5	0-38.5	27.5 (17.54-36)

Only control patients were included, patients with prophylactic mesh placement were excluded.

SSIH, stoma site incisional hernia; IQR, interquartile range.

*Range of SSIH percentages reported in studies.

†Median (IQR) of available information on reported median study follow-up since closure (months).

Table 5 Overview of studies reporting on prophylactic mesh placement for the prevention of SSIH

Author	Year	Design	Mesh or control	Method of closure		Control group	Outcome measure	SSIH detection method
				Mesh type	Mesh placement			
Bhangu	2014	CS	Mesh	Biological (Strattice™)	IPOM	None	30-day outcomes	~
Liu	2013	R	Mesh	Polypropylene (Ethicon Ultrapro®)	Onlay	~	Rate of SSIH	C and/or CT
			Control	~	~	Skin defect open		
Maggiori	2015	CM	Mesh	Bioprosthetic, non-cross linked collagen, porcine dermal matrix (Meccellis, Biotech)	Sublay, retromuscular	~	1-year rate of SSIH	CT
			Control	~	~	Primary closure		
van Barneveld	2013	CS	Mesh	Parietex™ Composite Parastomal mesh + AbsorbaTack™ (Covidien/Medtronic)	IPOM	None	SSIH and mesh complications	C and US

Continuous data are mean (standard deviation), mean (standard deviation, range), or median (interquartile range). C, clinical diagnosis; CT, computed tomography diagnosis; CS, case series; EI, end ileostomy; LC, loop colostomy; LI, loop ileostomy; m, months; R, retrospective; CM, case matched; IPOM, intraperitoneal onlay mesh; SSI, surgical site infection; SSIH, stoma site incisional hernia; US, ultrasound.

Table 5 continued

Number	Patients			Follow-up details			Number of stomas closed	Type of stomas	Number of SSIH (%)	Number of SSI (%)
	Males (%)	Age	BMI (kg/m ²)	Total	Time to closure	Time since closure				
7	~	~	~	30 days	~	30 days	7	LI, EI	0	1 (14.3)
47	63.8	69.6 (57.9-76.0)	>30, n=9	18.2m (11.7-30.8)	9.2m (4.1-15.0)	~	47	LI	3 (6.4)	2 (4.3)
36	58.3	65.0 (57.8-70.5)	>30, n=12	18.2m(11.7-30.8)	8.6m (4.1-15.1)	~	36	LI	13 (36.1)	1 (2.8)
30	60	61 (13, 25-79)	26 (4, 19-36)	16.8m(3.3, 11.4-23.9)	11 weeks (5, 5-26)		30	LI	1 (3.3)	2 (6.7)
64	62	61 (13, 28-84)	25 (4, 18-38)	39.2m(16.9, 14.9-79.7)	11 weeks (5, 2-27)		64	LI	12 (18.8)	1 (1.5)
10	40	66 (58-77)	25 (20-28)	~	6m (2-15)		10	LI, LC	0	1 (10)

Figures

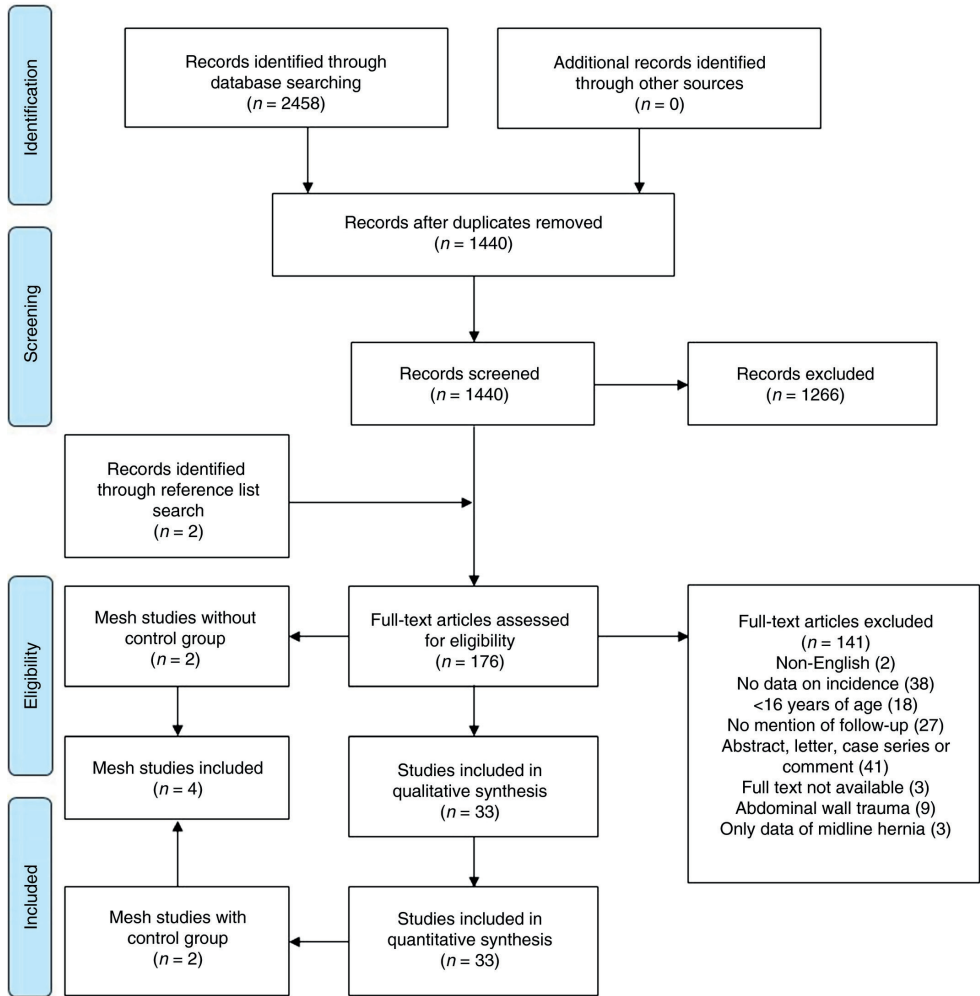


Figure 1 Preferred items for reporting of systematic reviews and meta-analyses (PRISMA) flow diagram.

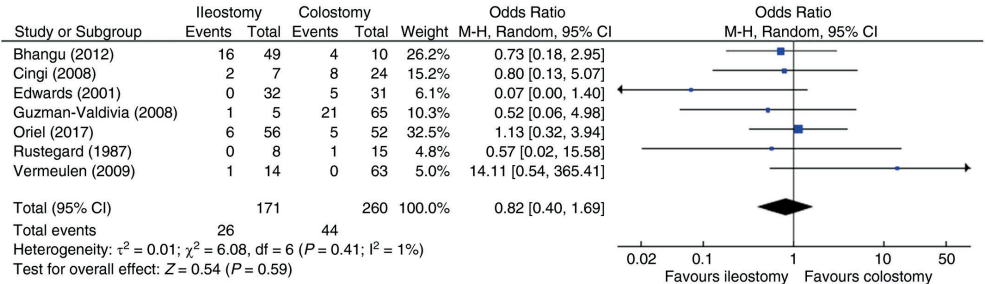


Figure 2 Forest plot of SSIH rates. M-H, random, Mantel–Haenszel random-effects model; df, degrees of freedom.

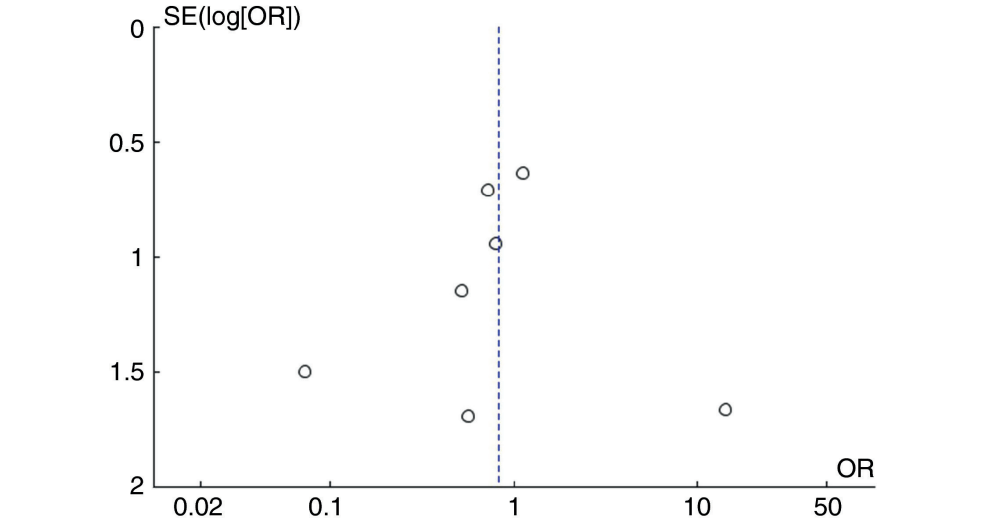


Figure 3 Funnel plot of the included studies

Appendix S1 Details of the search strategy

Search syntax per database:

Embase.com

('incisional hernia'/de OR 'hernia'/de OR 'abdominal wall hernia'/de OR 'complication'/mj OR 'postoperative complication'/mj OR (herni*):ab,ti OR complication*:ti) AND ('enterostomy'/exp OR (stoma OR stomal OR stomas OR enterostom* OR ileostom* OR colostom* OR jejunostom* OR duodenostom* OR cecostom* OR ostomy):ab,ti) AND ('abdominal wall closure'/de OR 'wound closure'/de OR (revers* OR close OR closed OR closing OR closure* OR 'take down' OR takedown OR ((former OR site) NEAR/3 stoma)):ab,ti)

Medline Ovid

("Incisional Hernia"/ OR "hernia"/ OR "Hernia, Abdominal"/ OR *")Postoperative Complications"/mj OR (herni*).ab,ti. OR complication*.ti.) AND (exp "Enterostomy"/ OR (stoma OR stomal OR stomas OR enterostom* OR ileostom* OR colostom* OR jejunostom* OR duodenostom* OR cecostom* OR ostomy).ab,ti.) AND (exp "Wound Closure Techniques"/ OR (revers* OR close OR closed OR closing OR closure* OR "take down" OR takedown OR ((former OR site) ADJ3 stoma)).ab,ti.)

Cochrane

((herni*):ab,ti OR complication*:ti) AND ((stoma OR stomal OR stomas OR enterostom* OR ileostom* OR colostom* OR jejunostom* OR duodenostom* OR cecostom* OR ostomy):ab,ti) AND ((revers* OR close OR closed OR closing OR closure* OR 'take down' OR takedown OR ((former OR site) NEAR/3 stoma)):ab,ti)

Web of science

((TS=(herni*) OR TI=complication*) AND TS=((stoma OR stomal OR stomas OR enterostom* OR ileostom* OR colostom* OR jejunostom* OR duodenostom* OR cecostom* OR ostomy)) AND ((revers* OR close OR closed OR closing OR closure* OR "take down" OR takedown OR ((former OR site) NEAR/2 stoma))))))

Google scholar

Hernia| Herniation|Hernias stoma|stomal|stomas|enterostomy|ileostomy|colostomy|jejunostomy|duodenostomy|cecostomy|ostomy reversal|close|closed|closing|closure|"take down"|takedown|"former stoma"| "stoma site"

Overview of number of articles per database before and after removal of duplicate articles:

Embase.com	1138	1112
Medline Ovid	649	150
Web of science	448	61
Cochrane	23	1
Google scholar	200	116
Total	2458	1440

Supporting information

Supplemental Table 1 SSIH repair rates (subdivided by stoma type)

Stoma group	Studies	Number of stomas closed	Number of SSIH detected	Number of SSIH repairs	Percentage of stoma closures needing SSIH repair	Range (%)*	Percentage of SSIH needing repair	Range (%)*
Loop colostomy	0	~	~	~	~	~	~	~
Loop ileostomy	9	865	90	51	5.9	0-12.5	56.7	0-100
End colostomy	2	42	4	3	7.14	0-15	75	0-100
End ileostomy	0	~	~	~	~	~	~	~
Colostomy	2	42	4	3	7.14	0-15	75	0-100
Ileostomy	10	945	94	53	5.6	0-12.5	56.4	0-100
Total	16	1152	138	71	6.1	0-38.4	51.4	0-100

Only control patients were included, patients with prophylactic mesh placement were excluded. SSIH = stoma site incisional hernia. *Range of SSIH percentages reported in studies.

Supplemental Table 2 Risk factors for SSIH

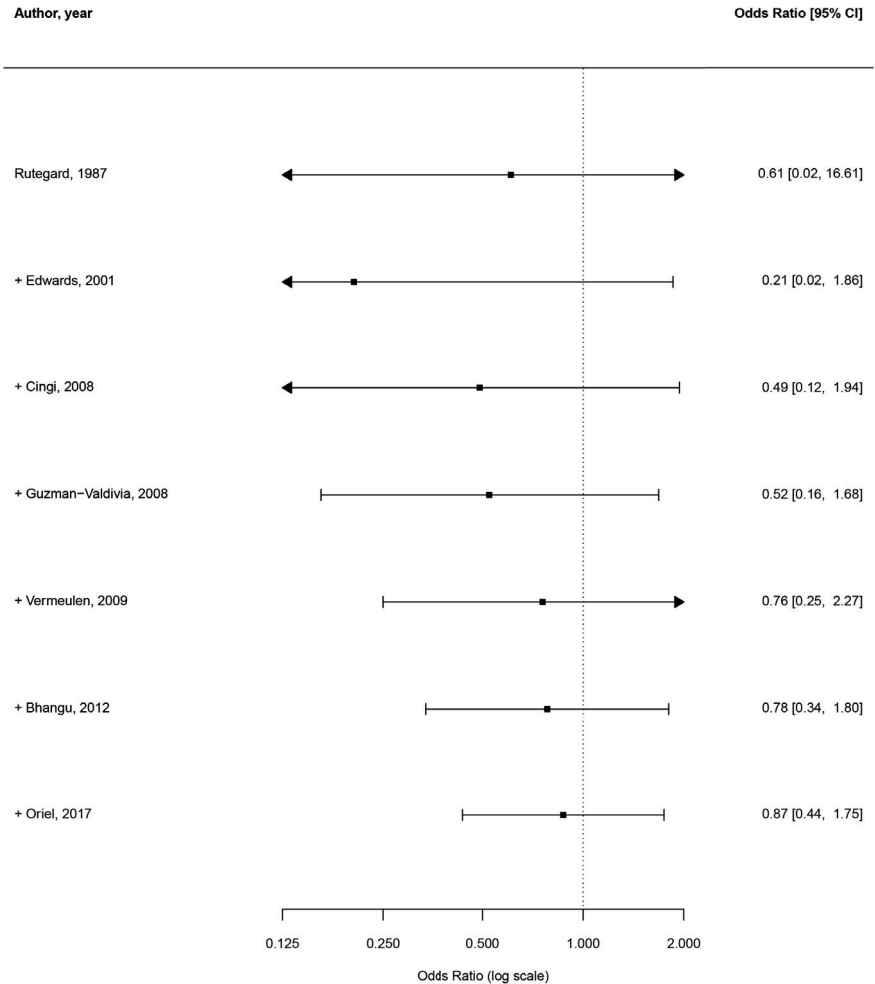
Author	Year	Risk factor(s) from univariate analysis	Risk factor(s) from multivariate analysis	Non-significant risk factors
Bhangu(30)	2012	~	~	- Age - Gender - Presence of MIH
Brook(5)	2016	- BMI - Hypertension (Stage 1; $\geq 140/90$ mmHg) - Overall incidence of postoperative complications	- BMI - Primary surgery for malignant disease	- ASA score - Time to ileostomy closure - Surgical approach (open or laparoscopic) - Urgency of primary surgery (emergency or elective) - Seniority of surgical supervision - Suture choice for rectal sheath defect (PDS or polypropylene) - Use of absorbable skin suture
Cingi(31)	2008	- Presence of MIH	~	- Age - Gender - BMI - SSI - Stoma type - Time to stoma closure
De Keersmaecker(32)	2016	~	~	- Age (<65 versus ≥ 65 years of age) - Gender - Diabetes mellitus - COPD - Heart failure - Surgical approach (open or laparoscopic) - Postoperative chemotherapy - Previous malignancy - Previous ventral abdominal hernia repair - Previous laparotomy - Previous inguinal hernia repair
Liu(45)	2013	- Age >60 years - Primary surgery for malignant disease - Diabetes mellitus - Chronic steroid usage - Chronic kidney injury	- Primary surgery for malignant disease - Diabetes mellitus - Mesh reinforcement (protective effect)	~

Author	Year	Risk factor(s) from univariate analysis	Risk factor(s) from multivariate analysis	Non-significant risk factors
Oriel(4)	2017	- Myofascial release at midline - Superficial incisional SSI	-	- COPD - Smoking - Diverticulitis - Time to stoma closure - Midline surgical approach - Presence of MIH at time of stoma reversal - Absorbable suture for trephine wound - Primary trephine wound closure - Presence of drain at trephine wound closure - Trephine fascial closure technique (interrupted or running) - Return to operating room - Systemic sepsis
Saha(3)	2009	- Reoperation after closure - Emergency primary surgery	-	-
Schreinemacher(52)	2011	-	- BMI (≥ 30 versus < 25 kg/m ²)	- Age - Gender - COPD - Smoking - Corticosteroid use - Diabetes mellitus - Underlying disease - Stoma type - Peritonitis at time of stoma creation - Time to stoma closure (< 6 months) - Suture material for closure of fascia - Open skin - Length of hospital stay after stoma closure - Number of prior laparotomies - History of hernia (parastomal, other, or combined) - Wound infection - Reoperation after stoma closure

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; MIH = midline incisional hernia; SSI = surgical site infection.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Edwards 2001	+	?	-	?	+	+	?
Hasegawa 2000	+	?	-	?	+	+	?

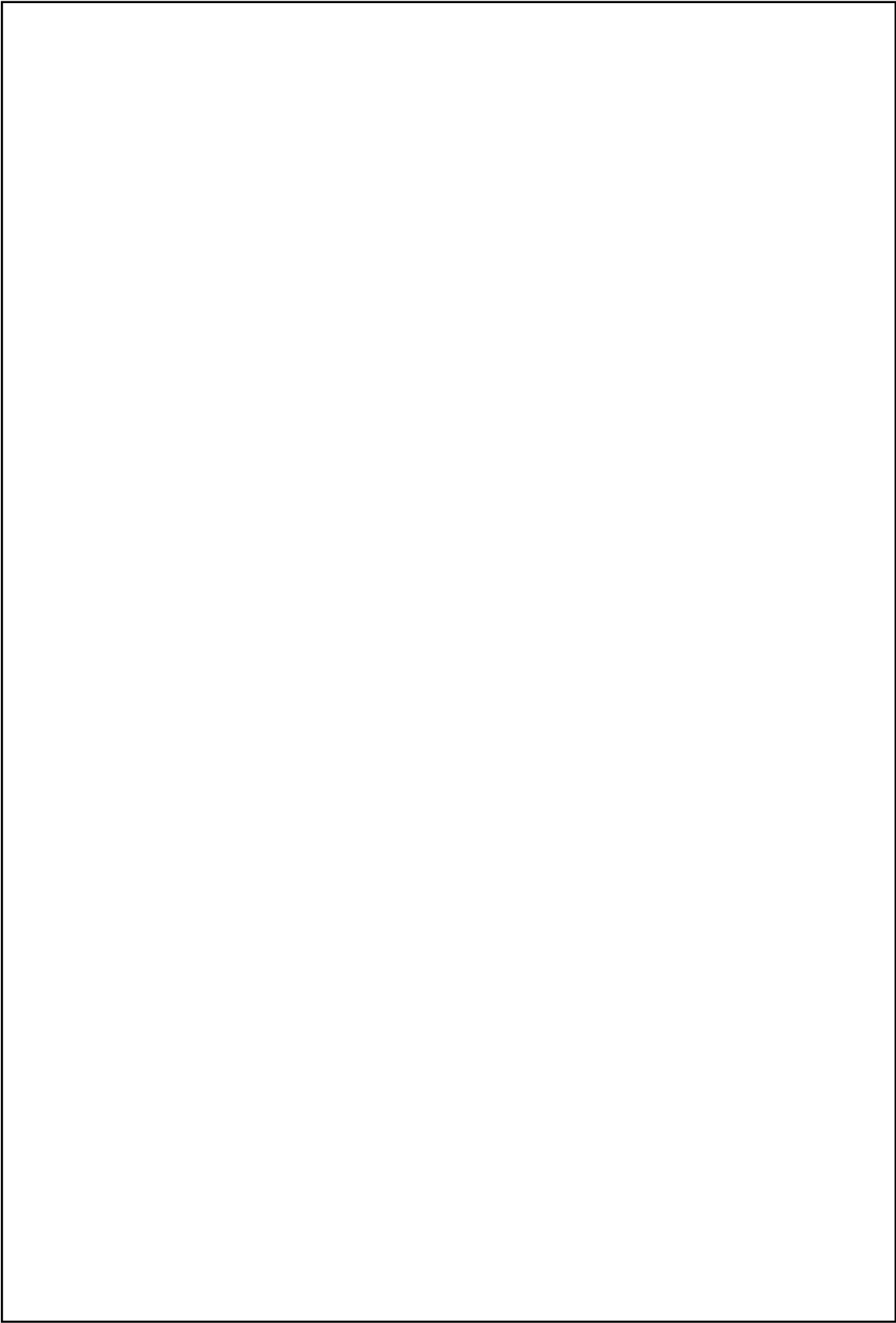
Supplemental Figure 1 Risk of bias assessment



Supplemental Figure 2 Cumulative meta-analysis of studies reporting on SSIH rates of ileostomies and colostomies

Part V

Prevention of postoperative ileus



Chapter 13

Nicotine chewing gum for the
prevention of postoperative ileus
after colorectal surgery -
a multicenter, double-blind,
randomised, controlled pilot study

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International Journal of Colorectal Disease 32.9 (2017): 1267-1275

Abstract***Purpose***

When postoperative ileus is not resolved after 5 days or recurs after resolution, prolonged POI (PPOI) is diagnosed. PPOI increases discomfort, morbidity and hospitalisation length, and is mainly caused by an inflammatory response following intestinal manipulation. This response can be weakened by targeting the cholinergic anti-inflammatory pathway, with nicotine as essential regulator. Chewing gum, already known to stimulate gastrointestinal motility itself, combined with nicotine is hypothesised to improve gastrointestinal recovery and prevent PPOI. This pilot study is the first to assess efficacy and safety of nicotine gum in colorectal surgery.

Methods

Patients undergoing elective oncological colorectal surgery were enrolled in this double-blind, parallel-group, controlled trial and randomly assigned to a treatment protocol with normal or nicotine gum (2 mg). Patient reported outcomes (PROMS), clinical characteristics and blood samples were collected. Primary endpoint was defined as time to first passage of faeces and toleration of solid food for at least 24 h.

Results

In total, 40 patients were enrolled (20 vs. 20). In both groups, six patients developed PPOI. Time to primary endpoint (4.50 [3.00–7.25] vs. 3.50 days [3.00–4.25], $p = 0.398$) and length of stay (5.50 [4.00–8.50] vs. 4.50 days [4.00–6.00], $p = 0.738$) did not differ significantly between normal and nicotine gum. There were no differences in PROMS, inflammatory parameters and postoperative complications.

Conclusions

We proved nicotine gum to be safe but ineffective in improving gastrointestinal recovery and prevention of PPOI after colorectal surgery. Other dosages and administration routes of nicotine should be tested in future research.

Introduction

Postoperative ileus (POI) is a temporary inhibition of gastrointestinal motility after abdominal surgery and is usually associated with nausea, vomiting, abdominal distension and lack of flatus and defaecation (1, 2). In more than 50% of cases, POI is not fully resolved in 4 days after the operation and when it does not resolve after 5 days or recurs after an apparent resolution, prolonged POI (PPOI) is diagnosed (3, 4). PPOI causes an increase in patient discomfort, morbidity, hospital-acquired infections, hospitalisation days and healthcare costs (5). The aetiology of POI is complex, with multiple factors contributing to its pathogenesis (6). Opioid use for postoperative analgesia is known to inhibit gastrointestinal transit and prolong POI (7, 8). However, the development of POI after abdominal surgery is mainly caused by intestinal manipulation during the surgical procedure, thereby triggering an inflammatory response and causing a sustained and generalised gastrointestinal hypomotility (7, 9, 10). Targeting this inflammatory response is of clinical relevance, but effective strategies are not yet available in clinical practice (8). The cholinergic anti-inflammatory pathway (CAIP) is one of the mechanisms that can be targeted for the prevention of POI. Experimental studies have shown that mediation of CAIP by vagus nerve stimulation can increase bowel motility and control inflammatory cell recruitment, by that preventing pathological changes important in the development of POI (1, 8, 11). Moreover, nicotinic acetylcholine receptors (nAChR) play an important role in mediation of CAIP, making nicotine an essential regulator of the pathway (11-13). Additionally, the $\alpha 7$ -nAChR also plays a role in nicotine-induced analgesia (14) and clinical evidence shows that preoperative transdermal and intranasal administration of nicotine significantly reduced postoperative opioid use (15, 16), while reducing opioids is an important strategy of shortening POI (1, 8, 17). Gum chewing is another important strategy, which has already been proven to be beneficial for gastrointestinal recovery after surgery. Several systematic reviews and meta-analyses have been published, supporting postoperative gum chewing in abdominal surgery (18-23). As a form of sham feeding, it mimics the cephalic phase of digestion and stimulates the gastrointestinal motility via neurohormonal and vagal pathways (18, 24). Combining perioperative gum chewing with the potential beneficial effects of nicotine leads to the hypothesis that nicotine gum chewing can reduce POI and improve postoperative outcomes (e.g. less morbidity and shorter length of stay) as well as reduce medical costs (25). The commercially available and inexpensive nicotine chewing gum may have a wide clinical application in POI prevention, by both stimulating the cephalic-vagal reflex and activating CAIP (Fig. 1). Therefore, we performed a multicenter, randomised, double-blind, controlled pilot study, comparing perioperative use of nicotine chewing gum with normal chewing gum, to assess the clinical efficacy and safety in patients undergoing colorectal surgery.

Methods

Study design and participants

This is a prospective, parallel-group, double-blind, randomised, controlled pilot study, conducted in the Havenziekenhuis, Rotterdam and the Sint Franciscus Gasthuis, Rotterdam. Adult patients who underwent an elective oncologic colorectal resection and gave written consent were included. Exclusion criteria were severe chronic cardiovascular disease or acute cardiovascular disease, severe liver- or kidney disease, oral or pharyngeal infection, esophagitis, hypersensitivity to any component of the nicotine gum, previous colorectal surgery, pregnancy, breast feeding, having an elevated risk of choking or being unable to chew gum for any reason.

Study procedures

Patients received either normal chewing gum or Nicorette® 2-mg chewing gum (2 mg/gum). This nicotine chewing gum is normally used as nicotine replacement therapy to help control craving for cigarettes and contains a low dose of nicotine. Patients had to chew the allocated chewing gum 2 h preoperatively and three times a day postoperatively, for half an hour at a time, until the first passage of faeces and tolerance of solid food for more than 24 h. Patients were asked to fill out a questionnaire before surgery and daily after surgery, until postoperative day (POD) 6. This patient diary contained questions regarding chewing gum use, oral intake, bowel movements, defaecation, gastrointestinal symptoms and visual analogue scale (VAS) pain score. Surgeons or surgical residents were asked to fill out case record forms (CRF) with information regarding both patient and surgical characteristics, such as age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, medication use, smoking, operative procedure, postoperative course and postoperative complications (e.g. anastomotic leakage (AL), surgical site infection (SSI), fascial dehiscence, urinary tract infection (UTI) and pneumonia).

Blood sample analysis

Peripheral blood samples were drawn from patients prior to the surgical procedure, and in the morning on POD1 and POD3. Measurements of plasma white blood cell count (WBC) and C-reactive protein (CRP) were performed by the hospital's laboratory at these same time points. Blood samples were centrifuged and plasma was stored at -80 °C. Enzyme-linked immunosorbent assays (ELISAs) were performed according to instructions of the manufacturer (PeproTech Inc., Rocky Hill, USA) to quantify the concentration of the systemic inflammatory marker interleukin-6 (IL-6).

A ratio of samples was calculated, through dividing the values of POD3 samples by those of the preoperative samples.

Outcome parameters

The primary study parameter was the time from surgery until the resolution of POI, defined as passage of faeces and toleration of solid food for at least 24 h (26). Secondary endpoints included time to first flatus, hospitalisation length, postoperative (infectious) complications, postoperative mortality, postoperative opioid use, patient

reported outcomes (e.g. pain score, nausea, regurgitations, vomiting, chewing gum use), inflammatory parameters (e.g. CRP, WBC and IL-6), blood pressure, body temperature and heart rate. PPOI was defined as POI that was not resolved after POD5 or recurrent POI after an apparent resolution of POI. Diagnosis of PPOI was not made directly by the participating surgeons, but via retrospective review of the patient diary and medical record, to ensure objectiveness of the primary endpoint.

Sample size calculation

According to Asao's gum chewing experiment (24) and Flood's nicotine trial (16), a sample size calculation was made, based on a mean POI time of 4.0 days in the chewing gum groups and an assumption of 2.6 days in the nicotine chewing gum group with a standard deviation of 1.5 days in both groups. In order to obtain a power of 80%, with an α level of 0.05, a number of 16 patients were needed in each group. As a dropout rate of 20% was expected, a total number of 40 patients (20 patients per group) were needed.

Patient allocation

Randomisation was done with Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) and results were placed and concealed in sequentially numbered, sealed, opaque envelopes by a person who was not connected to the trial. Patients were asked to participate by surgeons or specialised nurses who were involved in the trial. Patients were preoperatively randomised in a 1:1 design to either treatment with normal chewing gum or nicotine chewing gum. The allocated treatment was given to the patients by the nursing staff. Both patients and investigators were blinded for treatment allocation.

Statistical analysis

Only patients who completed the full study period were analysed. Data analysis was carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA, version 21.0 for Windows). Demographic data were presented in n (%) and median (interquartile range [IQR]). Categorical variables were compared using the Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test.

Results

In Fig. 2, the CONSORT flow diagram of the study is shown. Between January 29, 2015 and July 14, 2016, 62 patients were assessed for eligibility. Of these patients, 53 were randomly assigned to the normal chewing gum group or the nicotine chewing gum group. Two patients in each group withdrew from participation, because of disliking the chewing gum. One patient in the normal gum group was unable to continue treatment protocol, because of postoperative complications and ICU admission. The other patients withdrew for other reasons than disliking or being unable to chew the allocated gum. In total, 40 patients were included for data analysis.

Baseline patient and surgical characteristics were distributed evenly between both groups, without significant differences (Table 1). Urinary catheterisation failed in one

patient in the normal gum group and one patient in the nicotine gum group required vasopressors for hemodynamic support during surgery. All patients who were admitted to the intensive care unit (ICU) directly after surgery were transferred to the surgical ward after 1 day.

The time to primary endpoint (as defined earlier) as well as the time to first passage of faeces and flatus and length of stay (LOS) are given in Table 2. No statistically significant differences were found between groups. In both groups, six patients (30%) suffered from PPOI on or after POD6. Furthermore, there was no significant difference in the percentage of resolution of POI on POD1 to 5 (Table 3 and Supporting Information Fig. S1). In a subgroup analysis in which all four open procedures were excluded, the time to primary endpoint in the nicotine gum group was shorter, but also not significantly different from the normal gum group (3.00 days [3.00–4.50] vs. 4.50 [3.00–7.25], $p = 0.249$).

Six patients in the normal gum group and six in the nicotine group required a nasogastric tube during their postoperative stay. Three patients in the normal gum group and four in the nicotine gum group required total parental nutrition (TPN). Postoperative complications, reinterventions, readmissions and mortality during the first 30 days after surgery are given in Table 4. No differences were found between both treatment groups. Only one patient in the nicotine gum group had a short period of atrial fibrillation and overall, no myocardial infarction was seen. One patient in each treatment group required blood transfusion. One patient was readmitted because of anastomotic leakage and drainage of an intra-abdominal abscess, one patient was readmitted for adhesion ileus and one for observation of fever of unknown origin. One patient died during primary hospital stay, due to severe small bowel ischemia, caused by venous mesenteric thrombosis. Subgroup analysis for cases without intra-abdominal infectious complications during primary stay showed a time to primary endpoint of 4.00 days (3.00–5.50) vs. 4.50 (4.00–6.00) ($p = 0.339$) and LOS of 5.00 days (4.00–8.00) vs. 4.50 (4.00–6.00) ($p = 0.673$), for the normal gum and nicotine gum groups, respectively.

Postoperative opioid use

Fourteen patients in the normal gum group used oral opioids postoperatively, compared to 11 in the nicotine gum group ($p = 0.514$). Respectively, epidural opioids were used in 16 and 14 patients and a combination of oral and epidural opioids was used in 12 and 9 patients ($p = 0.527$). One patient in the normal group used a PCA pump and five patients in the nicotine gum group ($p = 0.091$). Patients in the nicotine gum group used epidural opioids for a significantly longer time (3.00 days [2.00–4.25] vs. 2.00 [1.00–.00], $p = 0.006$), but duration of oral opioid use did not differ between groups (1.00 day [0–3.50] vs. 1.00 [0–3.00], $p = 0.740$).

Patient reported outcomes

Fifteen patients who received normal gum filled out their diary, as compared to 16 patients who received nicotine chewing gum ($p = 1.000$). Pain scores (VAS) were significantly lower in the nicotine gum group on POD3 (1.40 [0.50–] vs. 2.70 [1.50–], $p = 0.007$), but did not differ on the other postoperative days (Supporting Information Fig. S2). No

differences were found in patient reported nausea, vomiting, regurgitations, abdominal distension and appetite (Supporting Information Fig. S3). Treatment compliance, as based on patient reported chewing gum use, is given in Supporting Information Table S1.

Inflammatory parameters

No significant differences were observed in IL-6 levels and white blood cell counts in preoperative samples and POD1 and three samples (Supporting Information Fig. S4). CRP levels differed on POD1 in the normal and nicotine gum groups, respectively (71.50 mg/L [35.00–92.75] vs. 94.50 mg/L [58.50–128.25], $p = 0.017$), but no differences were found in preoperative and POD3 samples (Supporting Information Fig. S4b). None of the calculated ratios showed differences between both groups (Table 5). On none of the postoperative days, a statistically significant difference was found in systolic and diastolic blood pressure, and heart rate (Supporting Information Fig. S5).

Discussion

This study was the first to investigate the role of nicotine chewing gum for the prevention of postoperative ileus by assessing its clinical efficacy and safety in patients undergoing elective colorectal surgery. By performing this parallel-group, double-blind, randomised, controlled pilot study, it was not possible to prove the beneficial effect of nicotine chewing gum, as compared to normal chewing gum. We hypothesised that the combination of perioperative gum chewing, with the potential beneficial effects of nicotine, could improve the resolution of POI, but although the median time to primary endpoint seemed shorter in the nicotine gum group (3.50 days vs. 4.50), the difference was not statistically significant. Moreover, an equal number of patients ($n = 6$) in each group suffered from PPOI and LOS did not differ significantly between both groups. Open procedures are known to worsen POI outcomes in colorectal surgery as compared to the laparoscopic approach (27). Ince all four open procedures in this study were in the nicotine gum group, a subgroup analysis was performed in which these four procedures were excluded. This showed an improvement in median time to primary endpoint (3.50 vs. 3.00 days) and length of stay (4.50 vs. 4.00 days) in the nicotine gum group, but although these open procedures influenced the outcomes, they did not provide a complete explanation for the lack of efficacy, since a significant difference between both groups was still not found.

A limitation of this study might be the relatively small sample size of 40 patients in total. However, our sample size calculation was based on the results of Asao et al. (24) who showed significant effects of chewing gum in a total of 19 patients. With a larger sample size than we initially calculated, we might have had more power to make a better distinguishment between the effects of sham feeding with normal chewing gum and the hypothesised additional effects of sham feeding with nicotine chewing gum.

Experimental studies have shown that a specific $\alpha 7$ -nAChR agonist (AR-R17779) ameliorates POI in rats and that stimulation of the $\alpha 7$ -nAChR improves survival of sepsis in rats (11, 28). Nevertheless, as clinical results of nicotine use for POI after

colorectal surgery were still lacking, the second aim of this pilot study was to evaluate the safety of nicotine chewing gum for the purpose of preventing POI. Because of concerns of systemic effects induced by nicotine administration, particularly cardiovascular complications (29), we decided to use Nicorette® 2 mg. This relatively low dose might have potentially been another reason for the lack of efficacy of the nicotine chewing gum in this study. However, the use of Nicorette® 2 mg in a perioperative setting of elective colorectal surgery, which has not been described in the literature before, seems to be safe.

No myocardial infarctions were registered in this study and only one patient had one short period of atrial fibrillation. This patient did receive nicotine chewing gum, but was known to have had previous episodes of paroxysmal atrial fibrillation. These findings are consistent with a previously published Cochrane Review, concluding that there is no evidence that nicotine replacement therapy increases the risk of heart attacks (30). Moreover, apart from cardiovascular complications, no differences were found in major and minor postoperative complications, reinterventions, readmissions and mortality between the normal and nicotine chewing gum groups. Overall, only one patient—enrolled in the nicotine chewing gum group—died during primary hospital stay on the 15th postoperative day. We did not consider usage of the nicotine chewing gum related to the cause of death, which was a result of intestinal ischemia caused by venous mesenteric thrombosis.

To combine the potential benefits of sham feeding with chewing gum and nicotine, we chose to use nicotine chewing gum in this pilot study. The reason being that this facilitated the possibility for a simple blinded comparison with normal chewing gum. However, a limitation of nicotine administration through chewing gum is that a sufficient release of nicotine is dependent on treatment compliance of the patient. All patients in this study were asked to report their use of chewing gum in the patient diary and it can be concluded that compliance to chewing the allocated gum is decreasing in the first three postoperative days. Conceivably, a more constant way of nicotine administration, such as the nicotine patches which Habib et al. (15) used in their study, might have given a more continuous release of nicotine.

If indeed the effective dose of nicotine would be too low in some patients, either due to low administered dose, insufficient exposure to the nicotine chewing gum or both, this might account for the absence of significant differences between the measured clinical and inflammatory parameters in both groups.

IL-6 and CRP levels, as well as WBC, were analysed in venous blood samples, as markers of the immune response, because it was hypothesised that this response would be less pronounced in patients in the nicotine chewing gum group. Overall lower levels of any of the three inflammatory parameters (IL-6, CRP and WBC) were not seen in this group and no differences were found, when compared to the normal chewing gum group, except for a significant difference of CRP levels on POD1. Sparreboom et al. (31) have concluded in their meta-analysis that levels of pro-inflammatory cytokines, such as IL-6, were higher in peritoneal samples as compared to serum samples after colorectal surgery, which might also explain why significant changes and differences were not detected in

our serum samples. Moreover, postoperative infectious complications, such as surgical site infections and pneumonia, could have affected the levels of these inflammatory parameters in both groups.

No differences in patient reported outcomes, such as nausea, vomiting, regurgitations, abdominal distension and appetite, were found. However, patient reported pain scores were significantly lower in the nicotine gum group as compared to the normal gum group on POD3 (1.40 [0.50-] vs. 2.70 [1.50-], $p = 0.007$). Although promising, this difference could partially be explained by the fact that patients in this group received epidural opioids for a significantly longer period of time (3.00 days [2.00–4.25] vs. 2.00 [1.00–.00], $p = 0.006$). However, the exact reason for a longer use of epidural opioids remains uncertain, since the decision to stop epidural anaesthesia in this study was made by the anaesthesiologist, who was blinded for patient allocation, with the aim to stop as early as possible, and preferably on or before POD2–3. These decisions were not registered prospectively. Furthermore, no significant differences in patient outcomes were found between both groups which might explain the extended requirement for epidural opioids in the nicotine gum group.

In conclusion, this study is the first to evaluate the potential beneficial role of nicotine chewing gum for another purpose than NRT in a randomised and double-blind clinical setting. Although the hypothesised potential benefits of nicotine chewing gum, as a cheap and readily available treatment option, seemed promising, no evident beneficial effects were found. This might be attributed to the sample size, the dose of the nicotine chewing gum and insufficient patient compliance to the allocated chewing gum. People in the nicotine chewing gum group seemed to experience less pain in the first three postoperative days, but a difference could only be proven on POD3. Therefore, more data on the effects of nicotine gum on bowel recovery after surgery are awaited (32). Furthermore, this study provides positive new insights on the safety of nicotine chewing in the setting of patients undergoing elective colorectal surgery. Future research should focus on other means of nicotine administration to patients undergoing colorectal surgery (e.g. patches), whether or not combined with normal chewing gum, and in higher doses, to further assess its effects on gastrointestinal recovery after colorectal surgery.

Acknowledgements

We thank all patients for their participation in this study, and all involved staff members for their efforts, in particular, A. de Boer, I. Sendar, A. van der Spek, W. Lee and A. van Duuren. This pilot study was funded by Stichting Coolsingel (Rotterdam, The Netherlands).

Compliance with ethical standards

In accordance with the Dutch law on medical research in humans, this study was approved by the Institutional Review Board of the Erasmus University Medical Center, Rotterdam, The Netherlands and the Institutional Review Boards of both participating hospitals. Patients gave their written consent after receiving oral and written information. This study was investigator initiated. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Tables

Table 1 Baseline patient and surgical characteristics in treatment groups

	Normal gum group (n=20)	Nicotine gum group (n=20)
Patient characteristics		
Sex		
Male	13 (65)	14 (70)
Female	7 (35)	6 (30)
Age (years)	67.50 [60.75-74.75]	69.00 [62.50-70.00]
BMI (kg/m ²)	26.91 [23.77-31.61]	25.02 [23.15-27.67]
Smoking	2 (10)	4 (20)
Diabetes mellitus	1 (5)	4 (20)
COPD	2 (10)	3 (15)
Cardiovascular disease	9 (45)	5 (25)
Corticosteroid use	3 (15)	1 (5)
Statin use	4 (20)	5 (25)
Neoadjuvant radiotherapy	1 (5)	0
Neoadjuvant chemoradiotherapy	1 (5)	0
Previous abdominal surgery	3 (15)	3 (15)
ASA Classification		
ASA I	4 (20)	3 (15)
ASA II	13 (65)	14 (70)
ASA III	3 (15)	2 (10)
ASA IV	0	0
Surgical characteristics		
Type of procedure		
Low anterior resection	3 (15)	3 (15)
Left hemicolectomy	3 (15)	2 (10)
Right hemicolectomy	8 (40)	6 (30)
Sigmoidectomy	5 (25)	6 (30)
Subtotal colectomy	1 (5)	0
Transverse colon resection	0	3 (15)
Laparoscopic approach	20 (100)	16 (80)
Anastomotic technique		
End-to-end	4 (20)	2 (10)
End-to-side	1 (5)	1 (5)
Side-to-end	5 (25)	5 (25)
Side-to-side	10 (50)	11 (55)
Anastomotic configuration		
Stapled	12 (60)	13 (65)
Sutured	8 (40)	8 (40)
Protective ileostomy	2 (10)	2 (10)
Nasogastric tube	12 (60)	13 (65)
Intraoperative complications	1 (5)	1 (5)
>50 mL blood loss	5 (25)	9 (45)
Duration of surgery (minutes)	133 [101-176]	117 [109-150]
Postoperative ICU admission	1 (5)	2 (10)

Data are median [IQR] or n (%).

BMI body mass index, *ASA* American Society of Anesthesiologists classification, *ICU* intensive care unit

Table 2 Time to primary endpoint, time to first passage of faeces and flatus, length of stay in days.

	Normal gum group (n=20)	Nicotine gum group (n=20)	p value
Time to primary endpoint (days)	4.50 [3.00-7.25]	3.50 [3.00-4.25]	0.398
Time to first passage of faeces (days)	3.00 [1.75-5.00]	3.00 [1.75-4.00]	0.414
Time to first passage of flatus (days)	1.00 [1.00-2.25]	1.00 [1.00-1.00]	0.454
Length of stay (days)	5.50 [4.00-8.50]	4.50 [4.00-6.00]	0.738

Data are median [IQR].

Table 3 Resolution of POI

	Normal gum group (n=20)	Nicotine gum group (n=20)	p value
Resolution of POI			
POD1	0	0	-
POD2	0	2 (10)	0.487
POD3	6 (30)	9 (45)	0.515
POD4	11 (55)	13 (65)	0.748
POD5	14 (70)	14 (70)	1.000
POD6 or later	20 (100)	20 (100)	1.000

Data are n (%).

Table 4 Postoperative complications, reinterventions (surgical and/or radiological), readmissions and mortality (≤ 30 days)

	Normal gum group (n=20)	Nicotine gum group (n=20)	p value
Atrial fibrillation	0	1 (5)	1.000
Fascial dehiscence	0	0	-
Colorectal anastomotic leakage	2 (10)	0	0.487
Intra-abdominal abscess	1 (5)	0	1.000
Myocardial infarction	0	0	-
Pneumonia	1 (5)	0	1.000
Surgical site infection	4 (20)	2 (10)	0.661
Urinary retention	0	1 (5)	1.000
Urinary tract infection	2 (10)	1 (5)	1.000
Reinterventions (<30 days)	4 (20)	2 (10)	0.661
Readmissions (<30 days)	3 (15)	0	0.231
Mortality (<30 days)	0	1 (5)	1.000

Data are n (%).

Table 5 Inflammatory parameters (Interleukin-6 (IL-6), C-reactive protein (CRP) and white blood cell (WBC) count)

	Normal gum group (n=20)	Nicotine gum group (n=20)	p value
IL-6 (pg/mL)			
Preoperative	1088.95 [529.65-1680.70]	1108.40 [547.18-1732.38]	0.663
POD1	881.80 [516.90-2138.70]	1047.65 [752.53-1930.10]	0.883
POD3	959.00 [648.90-2043.60]	987.40 [518.38-2139.75]	0.940
Ratio	1.13 [0.99-1.54]	1.12 [0.89-1.24]	0.517
CRP (mg/L)			
Preoperative	2.60 [1.00-4.75]	3.70 [2.25-23.38]	0.089
POD1	71.50 [35.00-92.75]	94.50 [58.50-128.25]	0.017
POD3	99.50 [76.25-179.50]	151.00 [101.75-188.50]	0.180
Ratio	45.83 [19.70-83.68]	33.92 [6.59-79.10]	0.180
WBC count (x 10⁹/L)			
Preoperative	7.10 [3.90-9.60]	6.60 [6.25-9.10]	0.477
POD1	12.30 [7.65-15.45]	12.30 [10.85-13.85]	0.865
POD3	8.50 [4.95-10.60]	9.00 [7.15-11.85]	0.583
Ratio	1.08 [0.95-1.59]	1.15 [0.99-1.77]	0.734

Data are median [IQR]

Figures

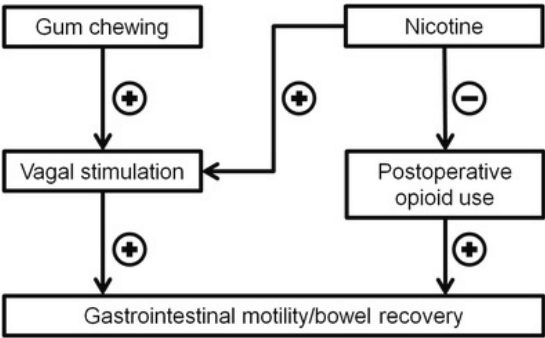


Figure 1 Simplified scheme of hypothesised effect mechanism of nicotine chewing gum

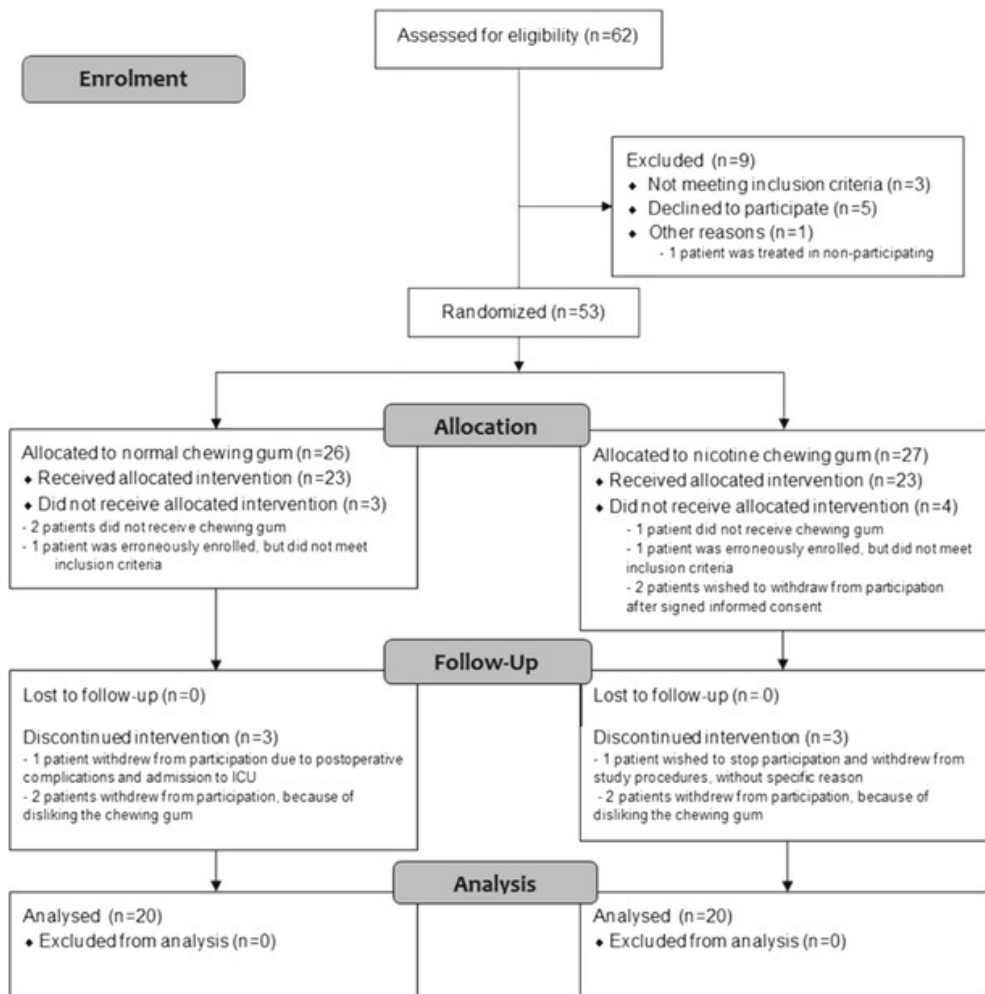
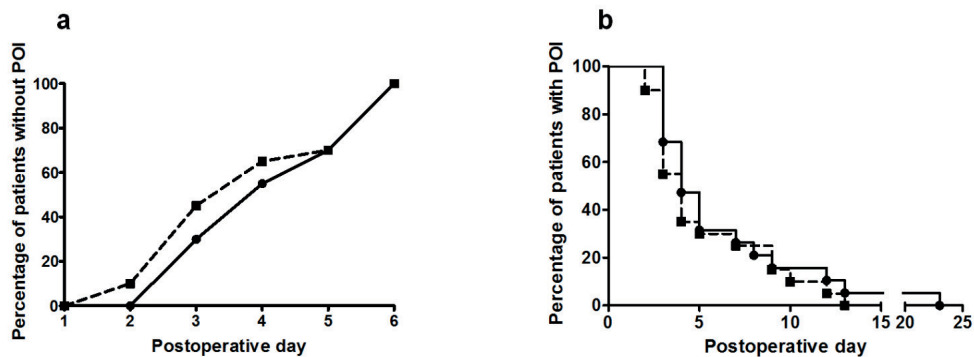


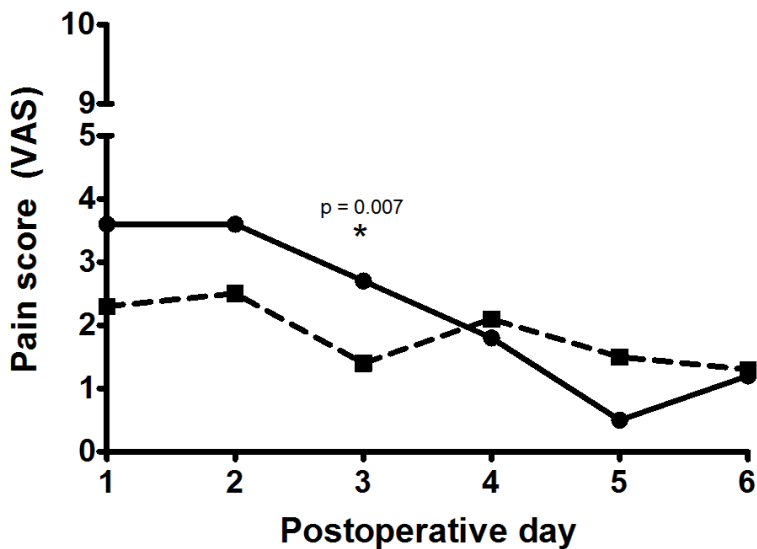
Figure 2 CONSORT flow diagram

Supporting Information

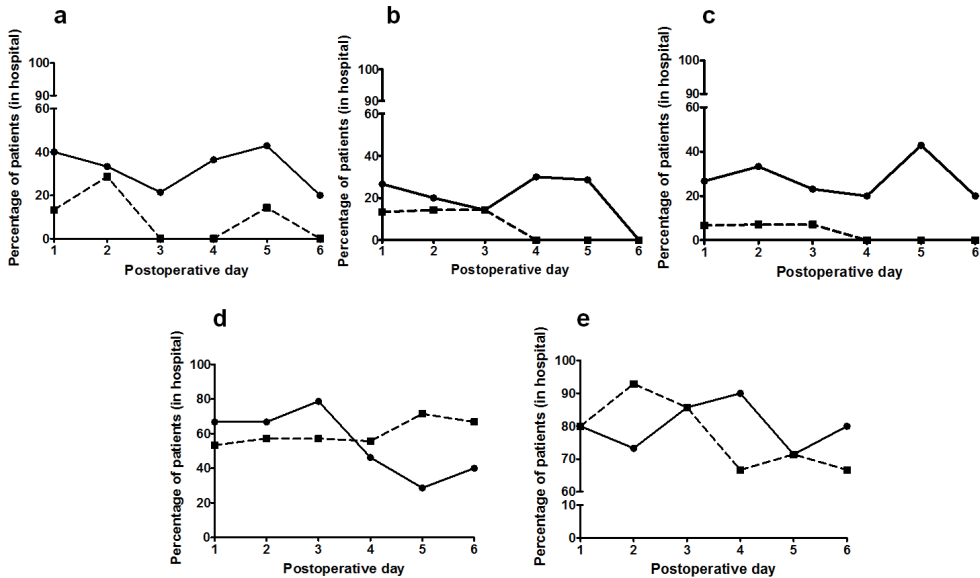
Normal gum = ● (dots), nicotine gum = ■ (squares)



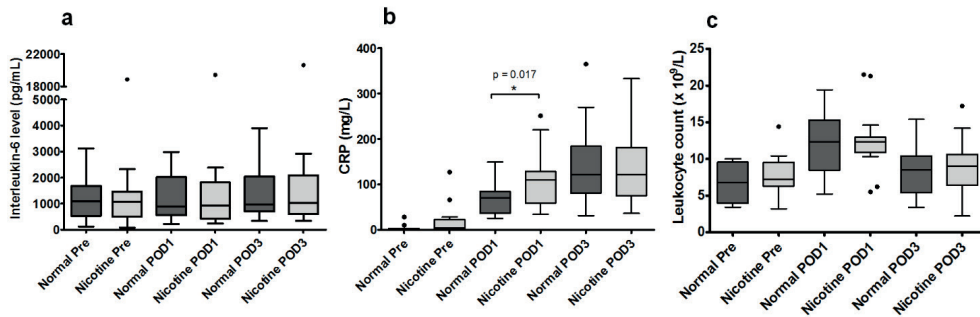
Supplemental Figure 1 Resolution of POI (A, B)



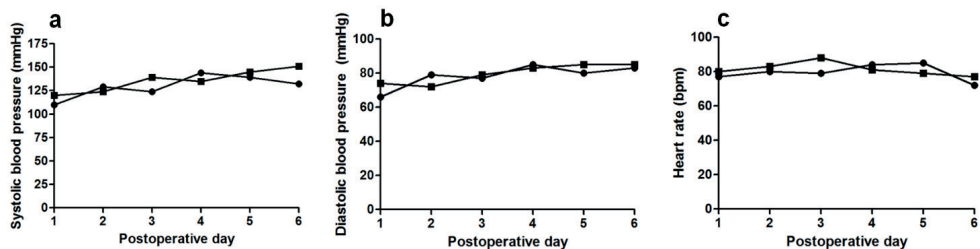
Supplemental Figure 2 Postoperative patient reported pain scores (Visual Analogue Scale)



Supplemental Figure 3 Postoperative patient reported outcomes: (A) Nausea, (B) Vomiting, (C) Regurgitations, (D) Abdominal distension, (E) Appetite



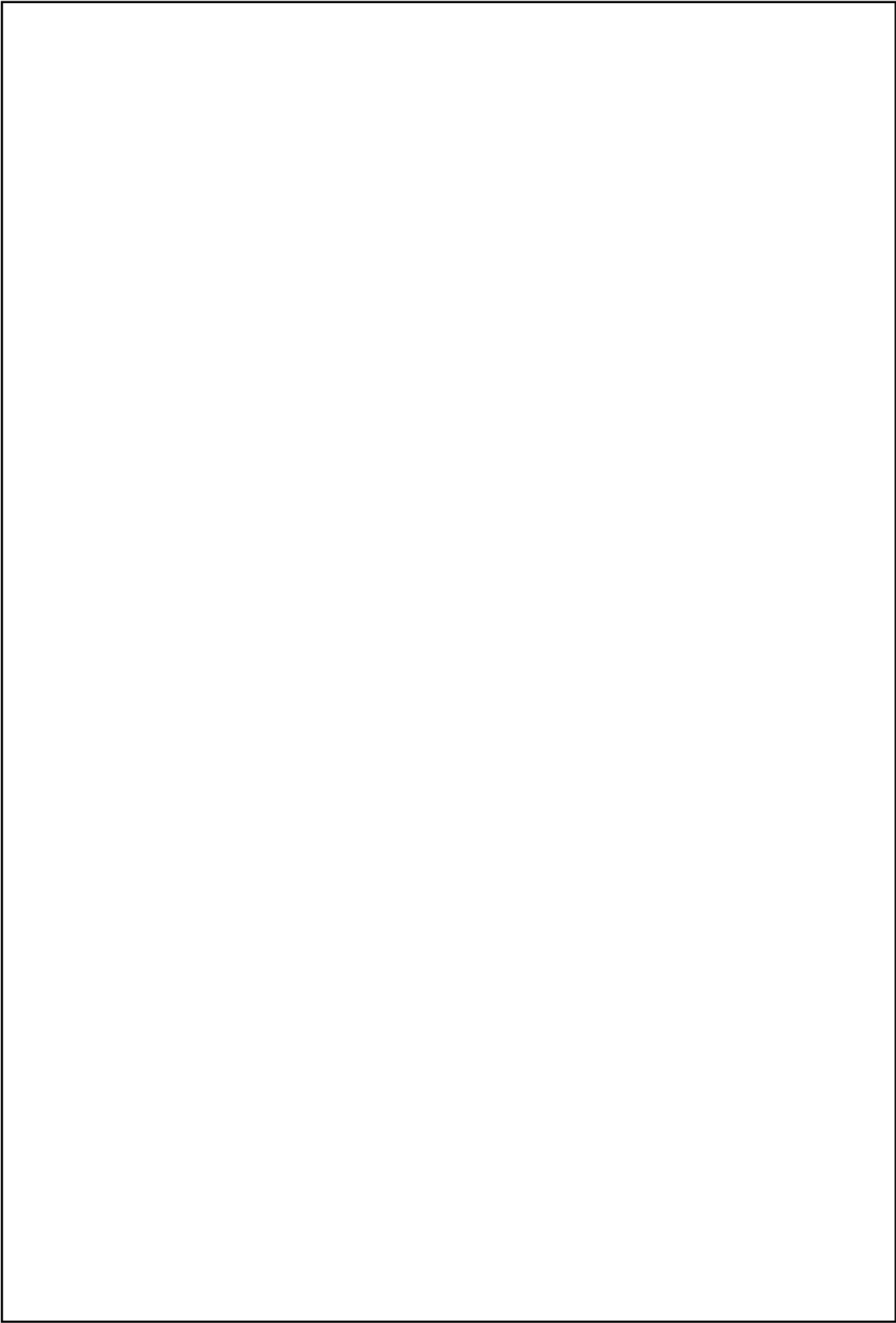
Supplemental Figure 4 Inflammatory parameters (A) Interleukin-6 (IL-6) levels, (B) C-reactive protein (CRP) levels, (C) white blood cell count



Supplemental Figure 5 Postoperative outcomes: (A) Systolic blood pressure, (B) Diastolic blood pressure, (C) Heart rate

Supplemental Table 1 Patient reported compliance to chewing gum

	Normal gum (n = 20)	Nicotine gum (n = 20)
POD1		
As in protocol	7 (35)	9 (45)
Less than protocol	5 (25)	4 (20)
More than protocol	2 (10)	2 (10)
Not reported	6 (30)	5 (25)
POD2		
As in protocol	7 (35)	7 (35)
Less than protocol	5 (25)	8 (40)
More than protocol	1 (5)	0
Not reported	7 (35)	5 (25)
POD3		
As in protocol	3 (15)	3 (15)
Less than protocol	11 (55)	13 (65)
More than protocol	0	0
Not reported	6 (30)	4 (20)
Data are n (%)		



Chapter 14

General Discussion and Future Perspectives

General Discussion

Over past decades, the treatment of complicated diverticulitis has gradually shifted towards a more conservative approach. This shift necessitates a tailored and evidence-based clinical assessment in order to choose the right treatment for the right patient. For this reason, the treatment of the different stages of complicated diverticulitis still remains a topic that is much debated. In this thesis, novel evidence was presented on both the non-resectional and resectional treatment of complicated diverticulitis with the aim to help elucidate some of these debated topics. In addition, this thesis also focused on complications related to the construction of a stoma, which might be the case during surgery for complicated diverticulitis, but, evidently, also for other benign or malignant colorectal disease. On the long term, the presence of a stoma puts patients at risk for the development of a parastomal hernia, or in case of stoma reversal, for a stoma site incisional hernia. Hence, the aim of this thesis was to contribute new insights on the incidence, diagnostics, and management of these stoma-related complications. Moreover, focus was put on the prevention of (prolonged) postoperative ileus, which is a potential short-term complication of colorectal surgery.

Part I Non-resectional treatment of complicated diverticulitis

Several options for the treatment of diverticular abscesses are at hand, such as surgery, abscess drainage, and antibiotics. Although treatment strategies have shifted from emergency surgery to non-surgical and non-resectional management, no clear consensus on their role yet exists (1). Importantly, conservative management might put patients at risk for adverse outcomes, both on the short and long term (2).

In **Chapter 2**, these short- and long-term outcomes, such as treatment failure, disease recurrence, and (emergency) surgery rates, were investigated in a retrospective, multicentre, cohort study of patients with CT-proven Hinchey Ib or II diverticulitis. Whereas previous studies were limited by sample size, short follow-up duration, single-institutional setting, or the lack of patient and disease characteristics, the present study tried to overcome these limitations (3-7). A total of 447 patients (Hinchey Ib 215; Hinchey II 232) were included and, after initial non-surgical management (antibiotics with (n=115) or without (n=332) percutaneous drainage), follow-up was available for a median period of 72 (interquartile range 55-93) months. From univariable analyses stratified by Hinchey grade, no differences were found between patients who were treated with or without drainage, in terms of short-term treatment failure, readmissions, emergency surgery, and mortality. In contrast, the short-term complication and long-term resection rates were higher for percutaneous drainage in Hinchey II patients. Even though they were stratified by Hinchey grade, these results might still partly be biased due to confounding by indication. Interestingly, however, multivariable analyses showed that the choice of treatment was not independently associated with short- and long-term adverse outcomes. Similarly, a more recent study from Finland also found that, despite adjustment for confounding, drainage did not seem to be superior to antibiotics alone (8). These potential confounders (e.g. patient and abscess characteristics) are of importance to consider, as these are factors that typically shape clinical decision-making.

In terms of these characteristics, another interesting finding was the fact that abscess sizes of ≥ 3 and ≥ 5 centimeter were demonstrated to be independent risk factors for short-term treatment failure and emergency surgery, respectively. Hence, in conclusion, it seems that abscesses of < 3 centimeter can be treated with antibiotics alone, on the premise that drainage can still be considered if there is no apparent clinical improvement. For patients with abscesses of ≥ 3 centimeter, close monitoring seems warranted and some restraint in the choice to drain seems justified.

In past decades, the role of non-resectional treatment by means of laparoscopic lavage for perforated diverticulitis with purulent peritonitis (Hinchey III) has increasingly been investigated (9-11). Similar to the conservative management of patients with diverticular abscesses, the sigmoid colon remains *in situ* and, hence, these patients are at risk for short-term treatment failure, as well as long-term disease recurrence, readmission, and surgery. In contrast to the potential risks, long-term benefits of laparoscopic lavage might be the avoidance of stoma construction and the subsequent risk of stoma-related and reversal-related complications. Although these long-term outcomes of laparoscopic lavage are an important factor in the debate on its added value to clinical practice, results were scarce and mostly limited to a 12-month follow-up (12-16).

The results presented in **Chapter 3** add novel evidence on the long-term consequences of laparoscopic lavage. Retrospective follow-up was conducted over a median period of 46 (interquartile range 7-77) months within a cohort of 38 patients who were initially treated with laparoscopic lavage. During this period, a total of 12 patients (32%) required additional surgery. Of the 32 patients who were alive and did not undergo a sigmoidectomy by the end of short-term (90-day) follow-up, seven (22%) eventually did undergo a sigmoidectomy. Also, in 31 patients who initially were successfully treated, recurrent diverticulitis or other complications occurred in 12 (31%). Although mostly descriptive and assessed in a relatively small cohort of patients, these results indicate that long-term consequences should not be underestimated. Of the three published randomized trials comparing laparoscopic lavage to sigmoid resection, only the DILALA has published results of a two-year follow-up period (13, 15-17). Within this period, it was found that lavage patients had a reduced risk of undergoing one or more reoperations as compared to the Hartmann's group (relative risk 0.55, 95%CI 0.36, 0.84)(17). These promising results might be strengthened by the long-term results of the SCANDIV trial and LOLA arm of the Ladies trial, which are awaited with interest (13, 15).

The long-term findings presented in this thesis and a wide range of other available evidence on laparoscopic lavage for the treatment of perforated diverticulitis were further discussed in **Chapter 4**, in which the question was posed 'when, how and if' laparoscopic lavage should be performed. One of the arguments against laparoscopic lavage is its higher risk for short-term adverse outcomes. However, it can be argued that these short-term risks are outweighed by potential benefits such as lower stoma and operation rates during further follow-up. Hence, minimizing short-term treatment risks is an important step towards the wider acceptance of lavage as a treatment option. In order to do so, accurate patient selection becomes even more crucial. An important step to improve this selection might be the optimization of pre- and intraoperative diagnostic

strategies to rule out diagnoses such as Hinchey IV disease or perforated colorectal cancer, such as CT imaging with rectal contrast or intraoperative sigmoidoscopy. Moreover, preoperative risk factors should be determined to distinguish between patients that might benefit most and patients at risk of treatment failure.

Part II Resectional treatment of complicated diverticulitis

In **Chapter 5**, the results of the DIVA arm of the international, multicentre, parallel-group, randomized, open-label, superiority Ladies trial were presented, in which the outcomes of sigmoid resection with primary anastomosis (with or without ileostomy) were compared to those of the Hartmann's procedure for patients with purulent or fecal peritonitis (Hinchey III or IV). Overall, 66 patients were included in the Hartmann's procedure group (Hinchey III 46, Hinchey IV 20) and 64 in the primary anastomosis group (Hinchey III 46, Hinchey IV 18). It showed the primary endpoint of 12-month stoma-free survival to be higher for primary anastomosis patients (94.6% [95% CI 88.7, 100] vs 71.7% [95% CI 60.1, 83.3], hazard ratio 2.79 [95% CI 1.86, 4.18]; log-rank $p < 0.0001$). No differences were found in the short-term morbidity and mortality rates, whereas results showed that primary anastomosis was favorable in terms of short-term reversal-related morbidity, as well as the time to stoma reversal and postoperative stay after reversal. Therefore, it was concluded that primary anastomosis is preferable to the Hartmann's procedure for hemodynamically stable, immunocompetent patients younger than 85 years with Hinchey III or IV diverticular disease.

Although this was not the first published trial to compare both procedures for this indication, it did have the largest sample size and several methodological advantages. Firstly, patients were randomized intraoperatively after diagnostic laparoscopy as opposed to the preoperative randomization in the other three trials (18-20). This allowed for a more accurate distinction between Hinchey grades, as this distinction is notoriously difficult to make based on CT imaging alone (21).

Secondly, even though no clear differences were identified, this trial was the first to assess patient-reported outcomes, in terms of general and gastrointestinal quality of life scores. Also, the present trial was the first to compare a sample of non-included patients with the included patient cohort. This is of importance, because despite the randomized study design, results might still have been biased by the exclusion of potentially eligible patients due to treatment preferences of both the surgeon or patient involved. Lastly, another methodological difference was the ability for surgeons to decide whether or not to construct a defunctioning ileostomy during the primary anastomosis procedure, which is an important benefit of this procedure as compared to the Hartmann's procedure.

As part of its design, the study did not only aim to assess patient-related outcomes, but also aimed to provide insights into the cost-effectiveness and cost-utility of both treatment groups. In **Chapter 6**, the results of the cost evaluation of the study were presented. The results showed that primary anastomosis was associated with significantly lower costs as compared to the Hartmann's procedure, with a mean difference in overall (direct and indirect) costs of €-8126 (95% CI -14660 to -1592). Moreover, primary

anastomosis was shown to be cost-effective in terms of the probability of being stoma-free and alive after 12 months (incremental cost-effect effectiveness ratio was €-39,094 (95% BCaCI -1,213 to -116). As the rates of acute diverticulitis and related admissions have been found to have increased over the course of the past decades, logically, the associated financial burden also increases (22, 23). Favorable cost-related outcomes, as demonstrated in the present cost evaluation, might serve as an additional argument to opt for primary anastomosis and might, as a consequence, help with its wider implementation in clinical practice.

In **Chapter 7**, a systematic review and meta-analysis of observational and randomized studies on the comparison of both procedures were presented. Based on these trial outcomes it provided arguments to prefer sigmoid resection with primary anastomosis over the Hartmann's procedure, such as favorable outcomes in terms of stoma reversal rates (OR 2.62, 95%CI 1.29, 5.31) and reversal-related morbidity (OR 0.33, 95%CI 0.16, 0.69), without a difference in mortality (OR 0.83, 95%CI 0.32, 2.19). Some authors stated that it seems to be the end of the Hartmann's era for perforated diverticulitis in light of all the accumulated evidence (24). However, it is of importance to acknowledge that this still might not apply to all patients with perforated diverticulitis and is in fact only true for selected patients. Indeed, the need for careful interpretation of the conclusions provided in the included studies and their application to the appropriate clinical setting were emphasized in the presented systematic review. In case of the included observational studies it should be noted that favorable outcomes of primary anastomosis might have been the result of confounding by indication. With regard to the randomized studies, it should be mentioned that the generalizability of their results largely depends on the applied in- and exclusion criteria, which - for example - led to the exclusion of hemodynamically unstable patients. Moreover, as stated before, these trial populations might also be subject to bias due to the non-inclusion of eligible patients. In addition to these results and notions, some of the knowledge gaps related to the surgical treatment of Hinchey III or IV disease were also identified in this chapter. Results from specific subgroups, such as patients undergoing primary anastomosis without ileostomy construction or Hinchey IV patients, were limited. Also, patient-reported and cost-related outcomes were scarcely reported, despite the fact that they might aid the further implementation of primary anastomosis into clinical practice.

Part III Treatment of (complicated) diverticulitis: appraisal of the evidence

In **Chapter 8**, a narrative review on the multidisciplinary management of complicated diverticulitis was presented. As the evidence on the various aspects of complicated diverticulitis and its management has progressed over recent years, the aim was to help guide clinicians by means of an extensive overview of the available literature on these aspects. The review discussed the several different treatment options and their indications and also focused on the epidemiology, classification, and diagnostics. These latter aspects have become increasingly important as they are paramount to facilitate accurate patient selection and, thus, to recognize the correct tailored approach for each individual patient.

In addition to evidence on the management of complicated diverticulitis, the guidelines of the European Society of Coloproctology that are presented in **Chapter 9** also focus on uncomplicated diverticular disease. These guidelines were the product of an international collaboration of surgical residents, PhD students, as well as expert clinicians from the fields of colorectal surgery, gastroenterology, and radiology. The multidisciplinary and evidence-based approach aided the development of guidance and recommendations on various topics related to all entities of diverticular disease, ranging from their etiology, diagnosis and follow-up to their (non-)surgical treatment and surgery-related technical considerations. Additionally, the development process helped to identify some of the remaining knowledge gaps and topics that can potentially be further elucidated in future research.

Part IV Stoma-related complications

Within the retrospective cohort study presented in **Chapter 10**, outcomes of the non-operative ‘watchful waiting’ strategy for parastomal hernia were compared to surgical treatment. It was found that 8 of the 38 patients (21%) who were treated non-operatively eventually underwent surgical treatment, of whom only one patient (2.6%) needed emergency surgery. Moreover, 23 of the 42 surgically treated patients (55%) had a recurrence over a median follow-up period of 46 months (i.q.r. 24-72), of whom 21 (91%) underwent an additional repair procedure. Given the relatively low cross-over and emergency surgery rate of non-operative treatment, it seems justified to opt for a non-operative treatment in patients with comorbidities and in those patients who are free of parastomal hernia symptoms, certainly within the light of the high recurrence rate after surgical treatment. The presented data facilitate the counseling of patients about the risks and benefits of both treatment strategies and, thus, support shared decision making. Evidently, the most important aim within the context of parastomal hernias is to optimize the prevention of occurrence. Consequently, a wide range of studies focusing on topics such as stoma construction and prophylactic mesh reinforcement have been published (25-28).

In the field of parastomal hernia research, it is of paramount importance to realize that several factors might affect reported incidence rates and that, therefore, these factors need to be acknowledged during the interpretation of these results and their potential translation into clinical practice. These factors include patient and stoma characteristics, length of follow-up, definition of parastomal hernia, as well as the choice of diagnostic modality (e.g. clinical examination, ultrasound, and CT imaging).

In **Chapter 11**, a systematic review was presented with the aim to compare these different modalities, as well as to assess and identify the different classifications and definitions used for parastomal hernias. Although the literature on this topic was heterogeneous and relatively scarce, a wide variance in the accuracy of the different modalities was found. Also, a large number of different definitions was identified, as well as studies in which a definition of parastomal hernia was not mentioned at all. Hence, the findings presented in this systematic review provide arguments to strive towards more consistency in the conduct and report of research on parastomal hernia. To improve the possibility of

comparing outcomes between clinical studies, the identification of a uniform parastomal hernia definition, such as the one proposed by the European Hernia Society (26, 29), might be required, in addition to the optimization of the report of diagnostic protocols within these studies. Evidently, the detection of parastomal hernia within the setting of research protocols might differ significantly from that in the everyday clinical context. Particularly, as in the latter context, symptomatic hernias and patient-reported outcomes play a much more important role.

Chapter 12 described the findings of a systematic review and meta-analysis on the incidence, risk factors, and prevention of stoma site incisional hernias. As for parastomal and incisional hernias, prophylactic mesh reinforcement has gained increased interest with regard to the prevention of stoma site incisional hernia. Results of the use of mesh during stoma reversal have been reported to reduce hernia rates (30). However, to further evaluate the potential beneficial role of prophylactic mesh, it is of importance to gain insights into the incidence of stoma site incisional hernia, as well as to identify patients that are at higher risk of developing such a hernia. The presented meta-analysis showed an overall rate of 6.5% (range 0%–38%, median follow-up 27.5 (17.54–36) months), which was 17.7% (range 1.7%–36.1%, median follow-up 28 (15.25–51.70) months) in the eleven studies that reported stoma site incisional hernias as primary endpoint. These figures also indicate the importance of reporting on outcomes assessment and its subsequent effect on incidence rates in the field of hernia research. In addition to the incidence rates, risk factors for stoma site incisional hernias were identified, which included diabetes, body mass index, and surgery for malignancy. The latter two factors were also found to be a risk factor in the cohort study by Amelung *et al.* (31), which identified stoma prolapse, parastomal hernia, and hypertension as additional independent risk factors.

Part V The prevention of postoperative ileus

In **Chapter 13**, the results of a randomized, double-blind pilot study comparing nicotine chewing gum with regular chewing gum for the prevention of (prolonged) postoperative ileus after colorectal surgery were presented. No clear differences were demonstrated in terms of prolonged postoperative ileus rates, postoperative and patient-reported outcomes, as well as inflammatory parameters. Hence, it was concluded that nicotine chewing gum seems to be safe but ineffective as preventative measure. Still, it might be worth exploring options such as sham feeding combined with nicotine patches, as these might improve compliance and provide a more constant nicotine administration. Nevertheless, due to the multifactorial etiology of postoperative ileus, several other measures that aim to prevent this common adverse outcome have been studied or are currently being investigated (32). Interestingly, reports of transcutaneous vagus or tibial nerve stimulation in humans have recently been reported to be feasible, although it should be acknowledged that these results are preliminary and require further evaluation (33, 34). As the burden of prolonged postoperative ileus is significant, research into improved or novel methods to reduce it should be supported and their results will hopefully help to further optimize existing enhanced recovery protocols.

Future Perspectives

Complicated diverticulitis

Throughout this thesis, the term ‘patient selection’ has been used several times. As the management of the different stages of complicated diverticulitis is shifting towards the use of less invasive and less extensive treatment options, this term becomes more and more important. Accurate assessment of both patient and disease characteristics is of paramount importance to be able to correctly identify the best treatment approach tailored for each individual patient.

To help facilitate patient selection, novel data on potential selection criteria and risk factors are needed. However, research into the emergency surgical setting and complicated diverticulitis is known to have some inherent difficulties to it. Firstly, the conduct of randomized controlled trials in critical and emergency care is known to be difficult (35, 36). In a relatively limited time span both patients and surgeons need to decide if they are willing to participate in the trial, which might subsequently lead to selection bias. In addition, trial awareness might in general also be limited in the emergency setting. Moreover, when interpreting results from prospective trials, the outcomes should only be interpreted within the context of the in- and exclusion criteria that were applied. At that point, population-based studies might be more useful, as they assess treatment outcomes from a broader perspective. Nevertheless, these studies are often limited by a short follow-up period, the lack of details on patient and disease characteristics, the absence of patient-reported outcomes, or a combination of these factors.

Thus, the challenge of future research is to find ways to overcome these methodological limitations. Ideally, new data should be gathered in the setting of a national or international, multicenter, prospective, observational design. Within this design, extensive details on patient and disease characteristics, as well as short- and long-term and patient-related outcomes should be gathered. This will enable both the identification of risk factors, with the possibility to adjust for potential confounders, but will also provide a reflection of treatment decisions and current clinical practice. Additionally, some of the remaining knowledge gaps – as identified in the meta-analysis presented in Chapter 7 – can be further elucidated, such as outcomes in perforated diverticulitis patients who undergo primary anastomosis without the construction of an ileostomy. Student- and trainee-led collaborative networks or collaborative study groups, such as the EuroSurg Collaborative and the Right Iliac Fossa Pain Treatment (RIFT) Study Group, are relevant examples of ways to conduct these types of studies (37, 38). In fact, efforts to assess the treatment and outcomes of complicated diverticulitis have recently been made by means of the DAMASCUS study, which is an international collaborative snapshot audit study (39).

In addition, the increasing centralization of colorectal surgery might have a beneficial effect on the ability to conduct research in the field of emergency colorectal surgery. The increase in clinical expertise, subsequent to centralization, might also lead to more engagement in the field of colorectal research. Hence, these centers of expertise will likely be more dedicated to the aid the conduct of clinical trials and cohort studies,

thereby increasing trial involvement and rates of patient enrollment, even in the setting of emergency surgical care. Moreover, in the future, the emerging role of the 'emergency (general) surgeon' might also come to positively influence both outcomes and research within the acute care setting (40-43).

Next to these novel studies and potential future research initiatives, new evidence can also be sought within existing trial designs and data. Examples include the long-term follow-up of studies such as the SCANDIV trial and the LOLA and DIVA arm of the Ladies trial. Moreover, combining individual data from trials might lead to new insights through post-hoc analysis of a larger sample of included patients. Indeed, an effort to combine data from the SCANDIV trial and LOLA arm of the Ladies trial is currently being undertaken and hopefully its results will provide useful evidence on the outcomes of laparoscopic lavage and risk factors for its potential failure.

Within the light of the published trials that compared primary anastomosis with the Hartmann's procedure for perforated diverticulitis, it should be noted that the majority of patients underwent open procedures. However, several studies have demonstrated that laparoscopic procedures also seem to be feasible in the setting of surgery for perforated diverticulitis and it has been suggested that laparoscopic emergency sigmoidectomy might even be superior in terms of less postoperative morbidity and a shorter hospital stay (44-46). Nevertheless, these studies should be interpreted with caution, as their conclusions might only apply to selected patients and require the need of experienced surgeons and optimal perioperative care (47, 48). Therefore, another future research direction might be to further investigate the role of laparoscopic emergency sigmoidectomy and, more specifically, the laparoscopic Hartmann's procedure. The latter procedure could be of interest for selected patients, as it might avoid some of the disadvantages of the open procedure and might facilitate a less complex (laparoscopic) reversal procedure.

However, importantly, future research should not only focus on the treatment of diverticulitis, but also on its prevention. In this regard, the increasingly investigated role of gut microbiota as part of the pathogenesis of diverticular disease might potentially be of clinical value (49). Although the existing evidence on this topic currently is relatively scarce, more studies seem to point towards a plausible role of the gut microbiome in relation to diverticulosis and diverticulitis (50). An increased understanding of the role of the microbiome in the pathogenesis of diverticular disease and disease progression will likely open up the way for less aggressive and patient tailored prevention and treatment approaches (51, 52).

Stoma-related complications

As stated in the general discussion of this thesis, within the literature on parastomal hernia increased attention has been put on the prevention of its occurrence, as well as patient-reported outcomes, which have rightfully come to play a more important role in research on stomas and stoma-related complications. Similarly to the before mentioned research initiatives, the CIPHER and PROPHER studies are two examples of research that focuses on these aspects (53, 54). The aims of the CIPHER study, a prospective observational cohort study conducted in the United Kingdom, are to investigate the

incidence of parastomal hernias during the follow-up after stoma construction, as well as to assess other complications and resource use. In addition, it also aims to assess the generic health status of included patients up to 24 months after index surgery. The PROPHER study, an international, prospective, observational cohort study, will be conducted to investigate outcomes of operative and non-operative parastomal hernia treatment in terms of patient-reported outcomes, such as quality of life, satisfaction, and decisional regret (54, 55). These research initiatives are awaited with great interest and will likely produce valuable results that are helpful for tailored prevention and treatment strategies, as well as shared decision-making.

Efforts have been made to come up with novel strategies to lower the occurrence and burden of colorectal anastomotic leakage. Consequently, these strategies might potentially decrease the need for protective ileostomy construction and might therefore help to decrease the rate of stoma-related and reversal-related morbidity. One such strategy is the use of intraluminal stents or sheaths, which has already been studied in a clinical setting (56). Within this context, investigators of the REPAIR research group (Department of Surgery, Erasmus University Medical Center) are currently setting up novel experimental models and studies to further investigate the effectiveness and safety of these measures.

Finally, with regard to the topic of stoma site incisional hernia, several trials have been designed to assess the effect of prophylactic mesh reinforcement to prevent hernia occurrence. One of these randomised trials, conducted by the Reinforcement of Closure of Stoma Site (ROCCS) Collaborative and West Midlands Research Collaborative, has shown that reinforcement of the abdominal wall with a biological mesh at the time of stoma closure reduced the rate of clinically detectable incisional hernia within 24 months after surgery (57). Additional data from other ongoing trials are also expected to provide novel evidence. The MEMBO, ILEOCLOSE, and LISTO trial all focus on ileostomy closure, whereas the ROCCS also included patients who undergo colostomy reversal (58-62). Certainly, within the light of future evidence, important factors such as quality of life and symptomatic hernias, the identification of specific risk groups, and economic implications should be investigated and taken into account (63).

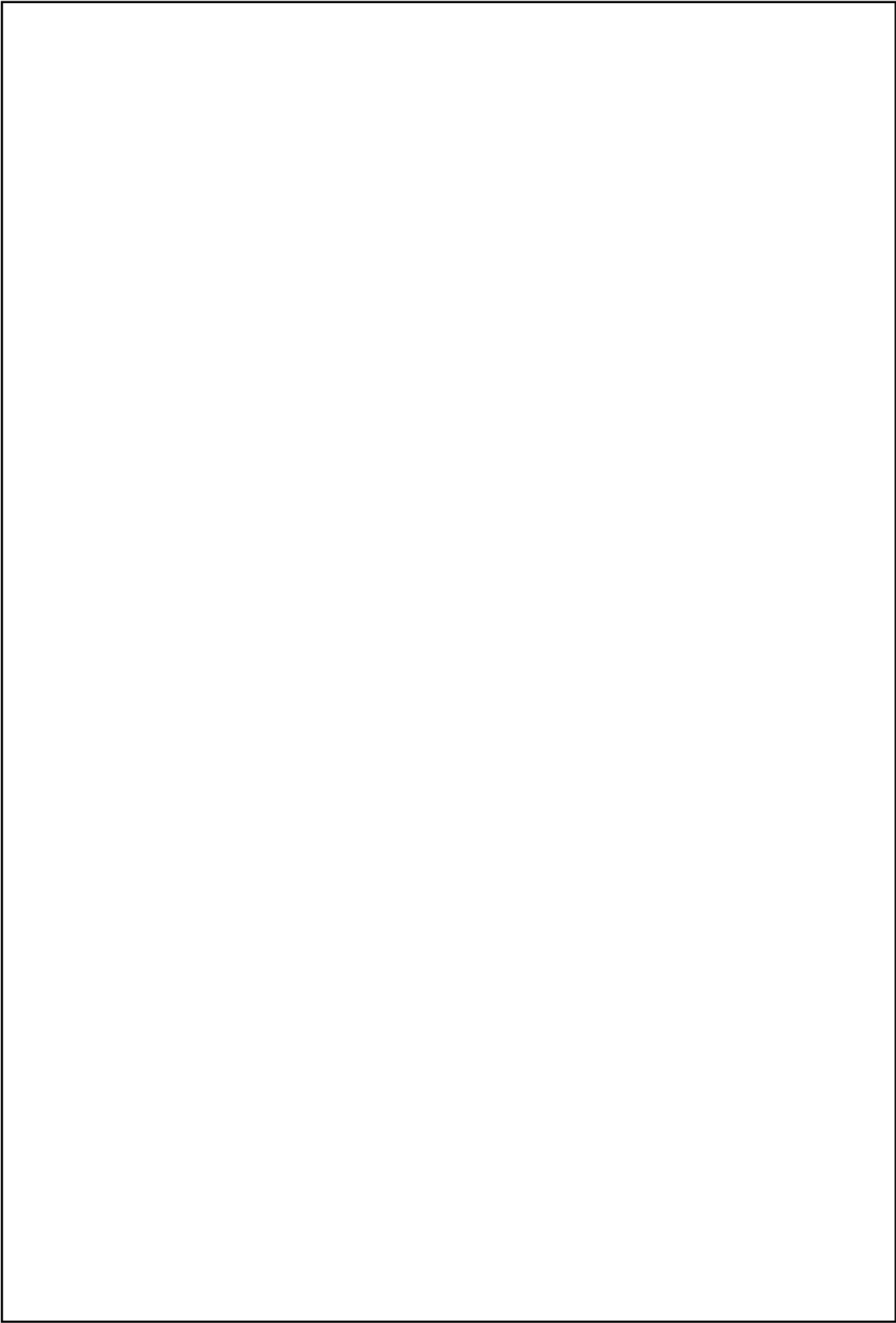
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Chapter 15

Summary

In this thesis, several aspects of the non-resectional and resectional treatment of complicated diverticulitis were assessed. Moreover, focus was put on the management and incidence of stoma-related complications, as well as on the prevention of postoperative ileus. A general introduction on these topics was provided in **Chapter 1**.

Part I describes the non-resectional treatment of complicated diverticulitis.

In **Chapter 2**, a multicentre, retrospective cohort study was presented, in which a total of 447 patients with a first episode of CT-diagnosed diverticular abscess (Hinchey Ib or II) were included in ten Dutch hospitals. Within this patient cohort, both short- and long-term outcomes of initial non-surgical management (antibiotics with percutaneous drainage (n=115, 25.7%) or without (n=332, 74.3%)) and risk factors for adverse outcomes were assessed. As stratified by Hinchey grade Ib or II, no differences in short-term treatment failure (Hinchey Ib: 22.3 vs. 33%, $p=0.359$; Hinchey II: 25.9 vs. 36%, $p=0.149$) and emergency surgery (Hinchey Ib: 5.1 vs. 6%, $p=0.639$; Hinchey II: 10.4 vs. 15%, $p=0.117$) were found between treatment groups, although Hinchey II patients undergoing percutaneous drainage had significantly more complications (12 vs. 3.7%, $p=0.032$). From multivariable regression analyses, it was derived that the treatment choice was not independently associated with short-term treatment failure (odds ratio (OR) 1.47, 95%CI 0.81-2.68), emergency surgery (OR 1.29, 95%CI 0.56-2.99), and long-term need for surgery (hazard ratio 1.08, 95%CI 0.69-1.69). Interestingly, it was found that an abscess size of ≥ 3 centimeter was associated with short-term treatment failure (OR 2.05, 95%CI 1.09-3.86) and of ≥ 5 centimeter with emergency surgery (OR 2.96, 95%CI 1.03-8.13). Hence, although these results did not show treatment choice to influence outcomes, they did seem to acknowledge that abscesses of ≥ 3 centimeter are at higher risk of adverse outcomes and warrant close monitoring.

In **Chapter 3**, long-term results of laparoscopic lavage as treatment for perforated diverticulitis were reported within a cohort of 38 patients who were included in ten Dutch hospitals. Follow-up was conducted over a median period of 46 months (interquartile range 7-77), in which recurrent uncomplicated and complicated diverticulitis, presence of a stoma, as well as (re)operations were assessed. It was found that in 12 patients, a total of 17 episodes of recurrent diverticulitis occurred, of which seven were complicated. A stoma could be avoided in 76% of all patients and in those patients with a stoma, it could be reversed in 78%. Also, 29 subsequent surgical procedures were reported in 12 patients, of which seven patients had at least undergone one emergency procedure. Interestingly, relevant events occurred up to six years after the lavage procedure.

In **Chapter 4**, an evidence-based answer to the questions ‘when, how, and if’ laparoscopic lavage should be performed was provided. After an introduction on complicated diverticulitis and a short overview of the history of surgical treatment for perforated diverticulitis, it describes the several technical perspectives, outcomes of randomized controlled trials, considerations on patient selection, and the conclusions and contradictions from the abundance of meta-analyses of studies reporting results of laparoscopic lavage in comparison to resectional treatment.

Part II covers the resectional treatment of complicated diverticulitis.

In **Chapter 5**, results of the DIVA arm of the Ladies trial, a multicenter, randomized, open-label, superiority trial on the surgical treatment of perforated diverticulitis with purulent or fecal peritonitis, were reported. The Hartmann's procedure and sigmoidectomy with primary anastomosis (with or without ileostomy) were compared in terms of 12-month stoma-free survival, morbidity and mortality after the index and reversal procedures, as well as quality of life. Eventually, outcomes of 66 patients in the Hartmann's procedure group and 64 in the primary anastomosis group were analyzed according to a modified intention-to-treat principle. The primary endpoint, 12-month stoma-free survival, showed to be significantly better for patients in the primary anastomosis group (94.6% [95% CI 88.7-100] vs. 71.7% [95% CI 60.1-83.3], hazard ratio 2.79 [95% CI 1.86-4.18]; log-rank $p < 0.0001$). In addition, no significant differences in short-term mortality (3% vs. 6%, $p = 0.44$) and overall morbidity (44% vs. 39%, $p = 0.60$) were found between Hartmann's procedure and primary anastomosis, respectively, whereas it was found that the short-term overall morbidity after stoma reversal was significantly lower for primary anastomosis (30% vs. 8%, $p = 0.023$). Therefore, it was concluded that primary anastomosis is preferable to Hartmann's procedure for the treatment of patients with perforated diverticulitis with purulent or fecal peritonitis, who are hemodynamically stable, immunocompetent, and younger than 85 years.

Chapter 6 described the results of the cost evaluation that was conducted within the DIVA arm of the Ladies trial. The overall total costs, including both direct and indirect costs, were €1,892,206 for the Hartmann's procedure group and €1,314,798 for the primary anastomosis group. For Hartmann's and primary anastomosis patients, the mean costs were €28,670 (95% CI 26,636 to 30,704) and €20,544 (95% CI 19,569 to 21,519), respectively. Subsequently, a difference in mean costs of €-8126 (95% CI -14660 to -1592) between both treatment groups was found, indicating primary anastomosis to be associated with significantly lower costs as compared to the Hartmann's procedure. In terms of the probability to be stoma-free and alive at the end of the 12 month follow-up, the incremental cost-effectiveness ratio was €-39,094 (95% BCaCI -1,213 to -116), demonstrating primary anastomosis to be cost-effective in comparison to the Hartmann's procedure.

In **Chapter 7**, a systematic review and meta-analysis of studies comparing the Hartmann's procedure to sigmoidectomy with primary anastomosis for patients with purulent or fecal peritonitis was presented. After an extensive systematic literature search of 1560 articles, a total of ten observational and four randomized studies were included. From the quantitative analyses of these studies, it could be derived that primary anastomosis was in terms of stoma reversal rates (OR 2.62, 95%CI 1.29, 5.31) and reversal-related morbidity (OR 0.33, 95%CI 0.16, 0.69), without a difference in mortality (OR 0.83, 95%CI 0.32, 2.19). These outcomes provide arguments to favor primary anastomosis over Hartmann's procedure in selected patients. Furthermore, a scarcity of evidence with regard to the cost-effectiveness and patient-reported outcomes of both procedures was identified, which are relevant outcomes to be addressed in future research.

Part III focuses on the synthesis of the available evidence on the treatment of diverticulitis.

Chapter 8 addressed the multidisciplinary treatment of complicated diverticulitis and provides a structured overview of the recent literature on a range of - often much debated - topics, such as nonoperative treatment options, the role of percutaneous drainage and laparoscopic lavage, as well as the resectional treatment of complicated diverticulitis. Moreover, an algorithm to help guide clinical decision-making was introduced.

Chapter 9 consists of the guidelines on diverticular disease as composed by the European Society of Coloproctology's (ESCP) guideline committee. Six working groups, consisting of clinical specialists (e.g. colorectal surgeons, gastroenterologists, and radiologists), residents and PhD students, were established and had the task to identify and assess the available evidence on a range of relevant topics. These general work group topics included the etiology of diverticular disease and its follow-up; imaging, indication, and classification; non-surgical management and dietary recommendations; emergency surgery; elective surgery; as well as technical considerations. Through several voting rounds, by members of the working groups and national representatives of all countries in the ESCP, proposed statements and recommendations were finalized.

Part IV consists of chapters that assessed stoma-related complications.

In **Chapter 10**, the nonoperative treatment of patients with a parastomal hernia was examined and compared to surgical treatment in a multicentre, retrospective cohort study in four Dutch hospitals. A total of 80 patients was included, of which 38 (48%) were treated nonoperatively and 42 (52%) underwent surgical treatment. The reasons for nonoperative treatment were assessed and were known in 24 patients (63%), being the absence of symptoms ($n=12$, 32%), comorbidities ($n=9$, 24%), and patient preference ($n=3$, 7.9%). During an overall median follow-up of 46 months (interquartile range 24-72), eight patients (21%) crossed over from nonoperative treatment to surgical treatment, of which one patient required emergency surgery. In the surgical treatment group, recurrence of parastomal hernia occurred in 23 patients (55%) and 21 of these patients (91%) underwent additional surgery. As the cross-over and emergency surgery rates of nonoperative treatment are relatively low, and the recurrence and re-repair rates of surgical treatment are high, it seems that patients without symptoms or with comorbidities might benefit most from the nonoperative 'watchful waiting' strategy.

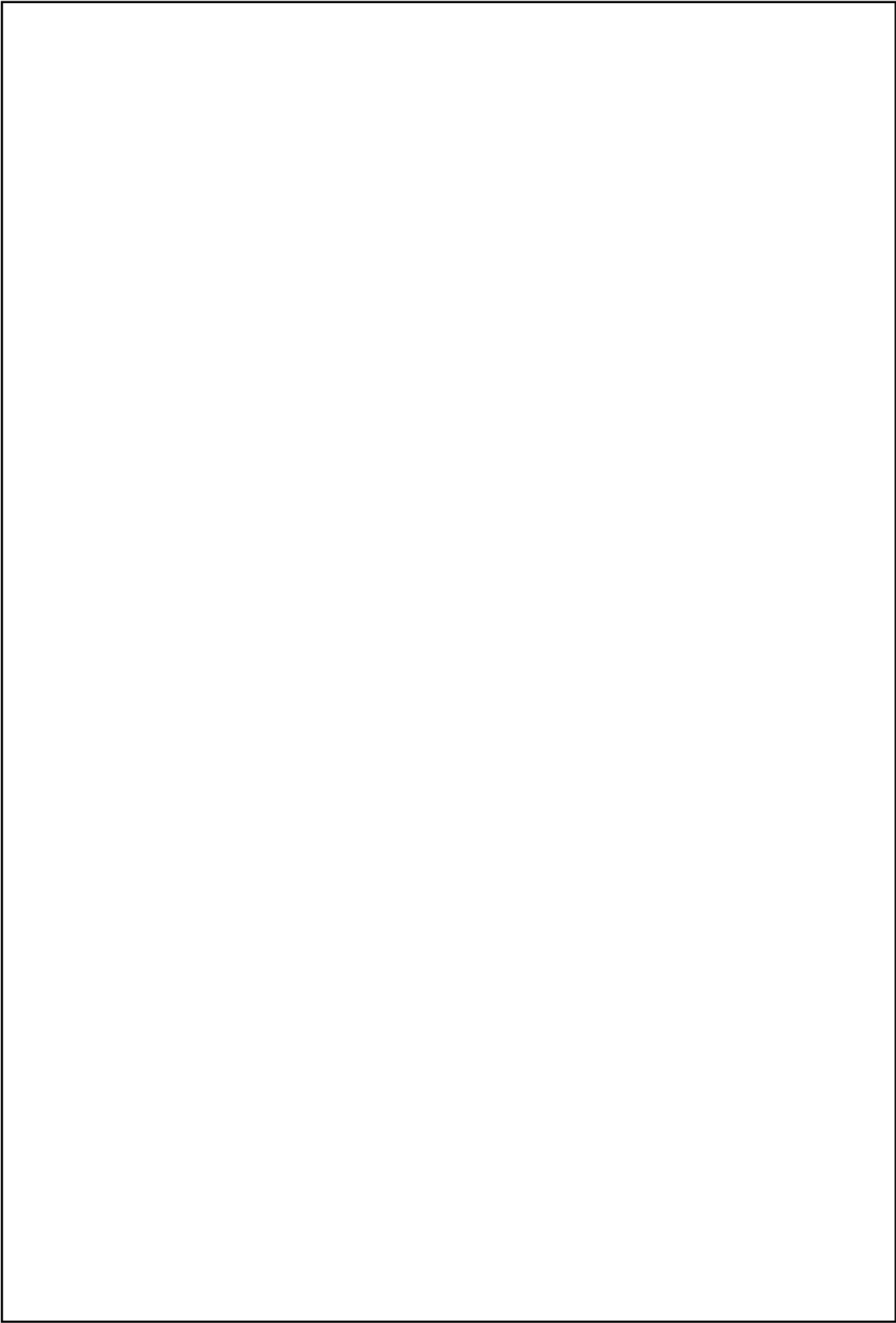
In **Chapter 11**, a systematic review on the different modalities for the diagnosis of parastomal hernia was presented. In a total of 29 included studies, diagnostic modalities such as ultrasound, CT scan, but also clinical examination were assessed and compared. In 19 studies, CT could be compared with clinical examination, which showed a relative difference in parastomal hernia incidence rates of 0.64 to 3.0 and, overall, 79% of the studies identified an increased incidence as compared to clinical assessment. Additionally, this review identified a wide range of definitions used throughout the literature. The results further emphasize the need for an accurate description of the diagnostic approach, definition, and classification in future research, as these might all affect the incidence of parastomal hernia.

In **Chapter 12**, the incidence, risk factors, and prevention of stoma site incisional hernias were assessed through the conduct of a systematic review and meta-analysis. From a total of 1440 identified articles, eventually, 33 studies were included that reported on the incidence of stoma site incisional hernias after stoma reversal. Eleven of the included studies assessed stoma site incisional hernia as primary endpoint and from these studies an incidence of 17.7% (range 1.7%–36.1%, median follow-up 28 (15.25–51.70) months) was derived. As extracted from all included studies, the incidence was 6.5% (range 0%–38%, median follow-up 27.5 (17.54–36) months). This indicates that the long-term complication of stoma site incisional hernia should not be underestimated. Furthermore, eight studies reported on risk factors, of which body mass index, diabetes and surgery for malignant disease were identified as independent risk factors. In addition, although two retrospective studies showed promising results for prophylactic mesh reinforcement as preventative method, data were limited and strong conclusions on its role could not be drawn.

Part V focuses on the prevention of postoperative ileus.

In **Chapter 13**, the results of a randomized, double-blind, pilot study on the efficacy and safety of nicotine chewing gum as compared to regular chewing gum for the prevention of postoperative ileus were described. In two Dutch centers, a total of 53 patients undergoing elective oncological colorectal surgery were enrolled. Eventually, outcomes were analyzed in 20 patients in both the nicotine chewing gum group, as well as the regular chewing gum group. No difference in primary endpoint, defined as time to first passage of feces and toleration of solid food for at least 24 hours, could be identified between both groups. For nicotine and regular chewing gum the median time to primary endpoint was 4.5 days (interquartile range, 3.0–7.25) vs. 3.5 days (3.0–4.25; $p = 0.398$), respectively. Similarly, no differences were found with regard to inflammatory parameters (C-reactive protein, white blood cell count, and interleukin-6) and patient-reported outcomes (e.g. pain scores and gastrointestinal symptoms). In addition, postoperative complications, reinterventions, and readmissions did not differ between both treatment groups. These results led to the conclusion that, within this pilot study, nicotine chewing gum seemed safe but ineffective in preventing postoperative ileus and improving gastrointestinal recovery.

In **Chapter 14** the findings of the presented studies were discussed and future perspectives were described.



Chapter 16

Samenvatting

Nederlandse samenvatting

In dit proefschrift kwamen verscheidene aspecten van de niet-resectie en resectie behandeling van gecompliceerde diverticulitis aan bod. Tevens werd aandacht besteed aan de incidentie van en het beleid bij stomagerelateerde complicaties, als ook aan de preventie van postoperatieve ileus. Een algemene introductie over deze onderwerpen werd beschreven in **Hoofdstuk 1**.

In **Deel I** werd de niet-resectie behandeling van gecompliceerde diverticulitis onderzocht.

In **Hoofdstuk 2** werd een multicentrische, retrospectieve cohortstudie gepresenteerd, waarin een totaal van 447 patiënten met een eerste episode van CT-gediagnosticeerde diverticulitis met abcesvorming (Hinchey Ib of II) werd geïncludeerd in tien Nederlandse ziekenhuizen. In dit cohort van patiënten werden zowel de korte- als langetermijntoekomst van de initiële niet-chirurgische behandeling (antibiotica met (n=115, 25.7%) of zonder (n=332, 74.3%) percutane drainage) als ook de risicofactoren voor ongewenste uitkomsten onderzocht. Na stratificatie voor Hinchey klasse Ib of II, werden geen verschillen gevonden in falen van de behandeling (Hinchey Ib: 22.3 vs. 33%, p=0.359; Hinchey II: 25.9 vs. 36%, p=0.149) en spoedchirurgie (Hinchey Ib: 5.1 vs. 6%, p=0.639; Hinchey II: 10.4 vs. 15%, p=0.117) op de korte termijn. Echter, Hinchey II patiënten die werden behandeld met percutane drainage hadden wel significant meer complicaties (12 vs. 3.7%, p=0.032). Uit een multivariabele regressie analyse kon worden afgeleid dat de keuze van behandeling niet onafhankelijk geassocieerd was met korte termijns behandelfalen (odds ratio (OR) 1.47, 95%CI 0.81-2.68) en spoedchirurgie (OR 1.29, 95%CI 0.56-2.99), en bovendien ook niet met chirurgische procedures op de lange termijn (hazard ratio 1.08, 95%CI 0.69-1.69). Daarentegen kon wel worden vastgesteld dat een grootte van het abces van ≥ 3 en ≥ 5 centimeter geassocieerd was met, respectievelijk, korte termijn behandelfalen (OR 2.05, 9%CI 1.09-3.86) en spoedchirurgie (OR 2.96, 95%CI 1.03-8.13). Ondanks dat in deze studie de keuze van behandeling de uitkomsten niet leek te beïnvloeden, leken de studieresultaten wel te bevestigen dat patiënten met een abces groter dan 3 centimeter een hoger risico op negatieve uitkomsten lopen en hun ziektebeloop dus nauwlettend dient te worden gevolgd.

In **Hoofdstuk 3** werden de lange termijn resultaten van laparoscopische lavage als behandeling voor geperforeerde diverticulitis weergegeven, zoals deze werden gevonden in een cohort van 38 patiënten die werden geïncludeerd in tien Nederlandse ziekenhuizen. De follow-up werd uitgevoerd over een mediane periode van 46 maanden (interkwartielafstand 7-77), waarin het aantal episodes van recidiverende ongecompliceerde en gecompliceerde diverticulitis, als ook de aanwezigheid van een stoma en (her)operaties werden vastgesteld. Bij 12 patiënten traden in totaal 17 episodes van recidiverende diverticulitis op, waarvan er zeven gecompliceerd waren. In 76% van de patiënten kon een stoma worden vermeden. Bij de patiënten bij wie toch een stoma moest worden aangelegd, werd het stoma in 78% van de patiënten later alsnog opgeheven. Voorts werden 29 chirurgische procedures geregistreerd bij een totaal van

12 patiënten, van wie zeven patiënten tenminste één spoedprocedure ondergingen. Relevante gerelateerde uitkomsten werden tot zes jaar na de lavage procedure nog gerapporteerd.

In **Hoofdstuk 4** werd een ‘evidence-based’ antwoord gegeven op de vragen ‘wanneer, hoe en of’ laparoscopische lavage uitgevoerd dient te worden. Na een introductie over gecompliceerde diverticulitis en een korte verhandeling over de historie van de chirurgische behandeling van geperforeerde diverticulitis, beschrijft het de verschillende technische perspectieven, uitkomsten van gerandomiseerde studies, overwegingen met betrekking tot patiëntselectie, als ook de conclusies en tegenstellingen zoals gevonden in de overvloed aan meta-analyses van de resultaten van studies die de resultaten van laparoscopische lavage hebben vergeleken met resectionele procedures.

In **Deel II** werd de resectionele behandeling van gecompliceerde diverticulitis onderzocht.

In **Hoofdstuk 5** werden de resultaten van de DIVA arm van de multicentrische, gerandomiseerde, open-label, superioriteitsstudie (Ladies) gepresenteerd, waarin de chirurgische behandeling van geperforeerde diverticulitis met purulente of fecale peritonitis werd onderzocht. De Hartmann procedure en sigmoïdrectie met primaire anastomose (met of zonder constructie van een ontlastend ileostoma) werden vergeleken in uitkomsten als de 12-maanden stomavrije overleving, morbiditeit en mortaliteit na de index- en ophefprocedure, als ook in termen van kwaliteit van leven. De uitkomsten van 66 patiënten in de Hartmann groep en 64 patiënten in de primaire anastomose groep werden vergeleken volgens het ‘modified intention-to-treat’ principe. Het primaire eindpunt, de 12-maanden stomavrije overleving, was significant beter voor patiënten in de primaire anastomose groep (94.6% [95% CI 88.7-100] vs. 71.7% [95% CI 60.1-83.3], hazard ratio 2.79 [95% CI 1.86-4.18]; log-rank $p < 0.0001$). Daarnaast werd geen verschil aangetoond in korte termijn mortaliteit (3% vs. 6%, $p = 0.44$) en totale morbiditeit (44% vs. 39%, $p = 0.60$) tussen respectievelijk de Hartmann procedure en primaire anastomose. Op de korte termijn na de ophefprocedure werd een significant lagere totale morbiditeit gevonden ten faveure van de primaire anastomose (30% vs. 8%, $p = 0.023$). Concluderend, werd dus gesteld dat de primaire anastomose de voorkeur verdient boven de Hartmann procedure voor de behandeling van hemodynamisch stabiele, immunocompetente patiënten van jonger dan 85 jaar, waarbij sprake is van geperforeerde diverticulitis met purulente of fecale peritonitis.

De resultaten van de kostenevaluatie van de DIVA-arm van de Ladies trial werden beschreven in **Hoofdstuk 6**. De totale kosten, bestaande uit zowel directe als indirecte kosten, waren €1,892,206 in de Hartmann groep en €1,314,798 in de primaire anastomose groep. Voor de Hartmann procedure en primaire anastomose waren de gemiddelde kosten per patiënt respectievelijk €28,670 (95% CI 26,636 tot 30,704) en €20,544 (95% CI 19,569 tot 21,519). Dit resulteerde in een gemiddeld verschil in kosten van €-8,126 (95% CI -14,660 tot -1,592) tussen beide behandelgroepen, waarbij sigmoïdrectie met primaire anastomose aldus significant met lagere kosten geassocieerd was. Voorts werd aangetoond dat, met betrekking tot de kans om stomavrij en in leven te zijn aan het einde van de 12-maanden follow-up, sigmoïdrectie met primaire

anastomose ook kosten-effectiever was, gezien een incrementele kosteneffectiviteitsratio van €-39,094 (95% BCaCI -1,213 tot -116).

In **Hoofdstuk 7** werden een systematische review en meta-analyse beschreven, waarin eveneens de vergelijking gemaakt werd tussen de Hartmann procedure en sigmoïdrectie met primaire anastomose voor patiënten met geperforeerde diverticulitis met purulente of fecale peritonitis. Na een uitgebreide systematische evaluatie van de literatuur werden, uit een totaal van 1560 gevonden artikelen, tien observationele en vier gerandomiseerde studies geïnccludeerd. Op basis van een kwantitatieve analyse van deze studies kon worden afgeleid dat de resultaten van een sigmoïdrectie met primaire anastomose beter zijn in het opzicht van het aantal opgeheven stoma's (OR 2.62, 95%CI 1.29, 5.31) en morbiditeit gerelateerd aan de ophefprocedure (OR 0.33, 95%CI 0.16, 0.69), zonder verschillen in mortaliteit (OR 0.83, 95%CI 0.32, 2.19). Deze uitkomsten bieden argumenten ten faveure van de primaire anastomose in geselecteerde patiënten. Eveneens werd er een lacune aan resultaten op het gebied van kosteneffectiviteit en patiënt-gerapporteerde uitkomstmaten geduid in de literatuur, hetgeen daarom relevante uitkomstmaten zijn voor toekomstig onderzoek.

In **Deel III** werd de nadruk gelegd op de samenvatting van het beschikbare wetenschappelijke bewijs over de behandelingsmogelijkheden voor diverticulitis.

Hoofdstuk 8 adresseerde de multidisciplinaire behandeling van gecompliceerde diverticulitis en biedt daarvoor een gestructureerd overzicht van de recente literatuur op een verscheidenheid van – vaak nog veel bediscussieerde – onderwerpen, zoals niet-operatieve behandelopties, de rol van percutane drainage en laparoscopische lavage, als ook de resectionele behandeling van gecompliceerde diverticulitis. Bovendien werd een algoritme voorgesteld ter ondersteuning van de klinische besluitvorming.

Hoofdstuk 9 bestaat uit de richtlijnen over diverticulitis, zoals deze zijn opgesteld door de richtlijncommissie van de European Society of Coloproctology (ESCP). Zes werkgroepen, bestaande uit medisch specialisten (e.g. colorectale chirurgen, radiologen en maag-, darm-, leverartsen) en onderzoekers op dit gebied, werden opgezet en kregen de taak toebedeeld om het beschikbare wetenschappelijke bewijs te beoordelen en een antwoord te geven op enkele vooraf gestelde onderzoeksvragen. De overkoepelende thema's van de werkgroepen waren: etiologie en follow-up van diverticulitis; beeldvorming, indicaties, en classificaties; niet-chirurgische behandeling en voedingsaanbevelingen; spoedchirurgie; electieve chirurgie; en technische overwegingen. Na meerdere stemrondes, met daarin de betrokkenheid van werkgroepleden en nationale vertegenwoordigers van alle landen betrokken bij de ESCP, werden de voorgestelde conclusies en aanbevelingen afgerond.

In **Deel IV** werd aandacht besteed aan stomagerelateerde complicaties.

In **Hoofdstuk 10** werd de non-operatieve behandeling van patiënten met een parastomale hernia onderzocht en vergeleken met de chirurgische behandeling door middel van een multicentrische, retrospectieve cohortstudie die werd uitgevoerd in vier Nederlandse ziekenhuizen. In totaal werden 80 patiënten geïnccludeerd, van wie er 38 (48%) non-

operatief en 42 (52%) chirurgisch werden behandeld. De redenen om te kiezen voor een non-operatieve behandeling werden bestudeerd en waren voor 24 patiënten (63%) bekend, te weten: afwezigheid van symptomen ($n=12$, 32%), co-morbiditeit ($n=9$, 24%) en een voorkeur van de patiënt ($n=3$, 7.9%). Gedurende een mediane follow-up periode van 46 maanden (interkwartielafstand 24-72) was er sprake van 'cross-over' van non-operatieve naar chirurgische behandeling in acht patiënten (21%), bij wie er in één geval sprake was van een spoedprocedure. In de chirurgisch behandelde groep was er sprake van een recidief parastomale hernia bij 23 patiënten (55%), van wie 21 patiënten (91%) nogmaals een chirurgische procedure ondergingen. Gezien het relatief lage aantal 'cross-overs' en spoedoperaties in de non-operatieve groep en juist de hoge percentages recidieven en re-operaties, lijkt een non-operatieve 'watchful waiting' strategie voor patiënten zonder klachten of met co-morbiditeit acceptabel te zijn.

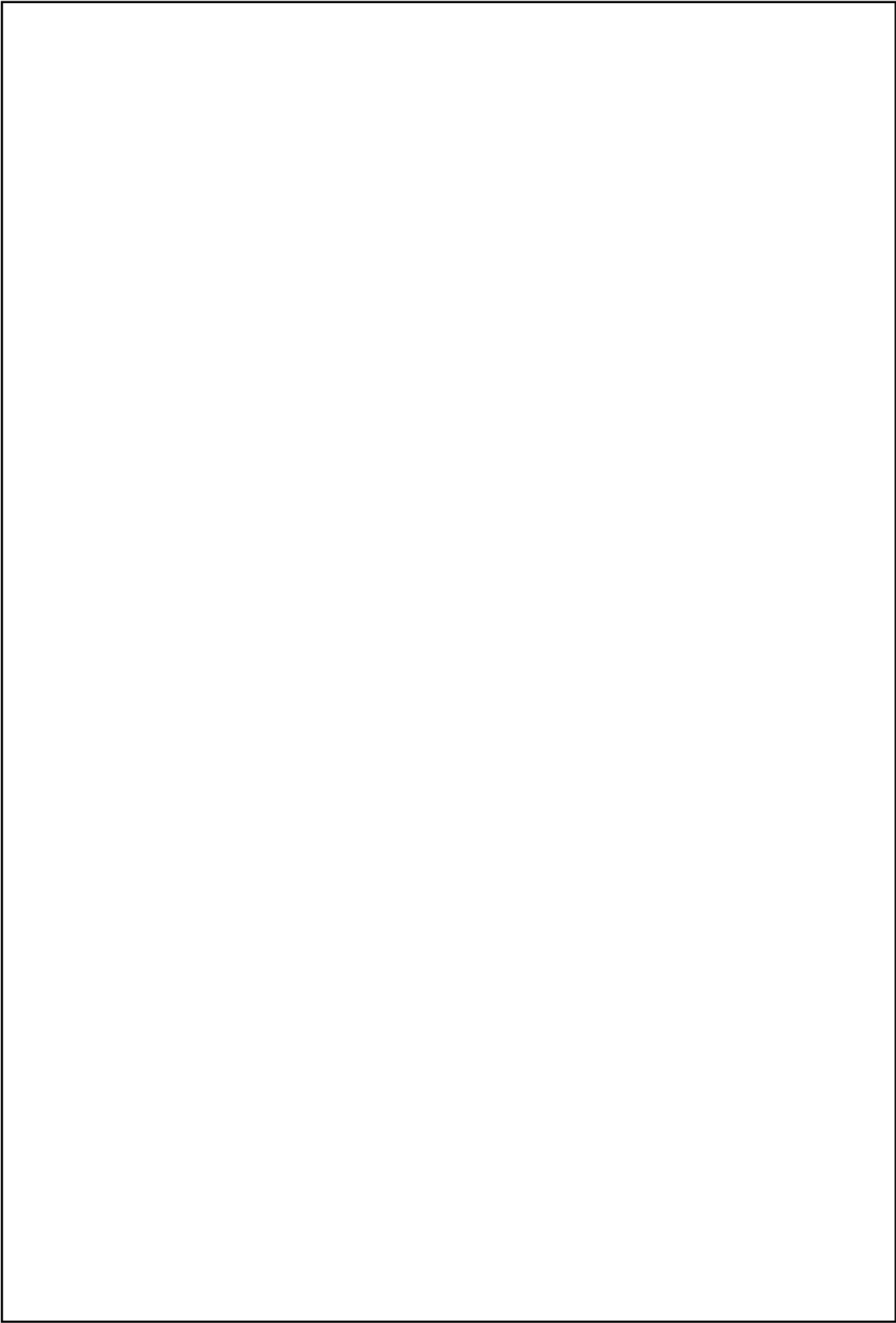
In **Hoofdstuk 11** werd een systematische review over de verschillende diagnostische modaliteiten voor de diagnosestelling van parastomale hernia's beschreven. Voor een totaal van 29 studies werden modaliteiten zoals echografie, CT-scan, als ook lichamelijk onderzoek geduid en vergeleken. Diagnostiek door middel van CT-scan kon in 19 studies worden vergeleken met lichamelijk onderzoek, waarbij een relatief verschil in de detectie van parastomale hernia's werd gevonden variërend van 0.64 tot 3.0 en tevens was er sprake van een toegenomen detectie ten opzichte van lichamelijk onderzoek in 79% van deze studies. In aanvulling hierop werd ook een groot aantal verschillende definities van parastomale hernia's in de geïnccludeerde studies geconstateerd. De beschreven resultaten benadrukken de noodzaak van een eenduidige beschrijving van de diagnostische benadering, definitie, en classificatie van parastomale hernia's in toekomstig onderzoek, aangezien al deze factoren de incidentie kunnen beïnvloeden.

In **Hoofdstuk 12** werden de incidentie, risicofactoren en preventie van stomalittekenbreuken – zijnde littekenbreuken op de plek van een reeds opgeheven stoma – onderzocht door middel van een systematische review en meta-analyse. Vanuit een totaal van 1440 geïdentificeerde studies werden 33 studies geïnccludeerd die de incidentie van stomalittekenbreuken beschreven. In elf van de geïnccludeerde studies was de incidentie van stomalittekenbreuken daadwerkelijk het primaire eindpunt en op basis van deze studies werd een incidentie van 17.7% (range 1.7%–36.1%, mediane follow-up 28 (15.25–51.70) maanden) gevonden. Tevens kon een incidentie van 6.5% (range 0%–38%, mediane follow-up 27.5 (17.54–36) maanden) worden afgeleid uit alle geïnccludeerde studies. Deze percentages geven aan dat het probleem van stomalittekenbreuken op de lange termijn niet onderschat dient te worden. In aanvulling op deze resultaten, konden uit acht studies ook risicofactoren worden afgeleid, waarbij BMI, diabetes en chirurgie voor een maligniteit als onafhankelijke risicofactoren werden geïdentificeerd. In twee retrospectieve studies werden veelbelovende uitkomsten gevonden van profylactische meshversterking ter preventie van een stomalittekenbreuk, echter deze resultaten waren gelimiteerd en boden daarom nog weinig ruimte voor stevige conclusies over de rol en toegevoegde waarde van meshversterking.

In **Deel V** werd de preventie van postoperatieve ileus beschreven.

In **Hoofdstuk 13** werden de resultaten van een gerandomiseerde, dubbelblinde pilotstudie gepresenteerd, waarin de effectiviteit en veiligheid van nicotine kauwgum werden vergeleken met normale kauwgum ter preventie van postoperatieve ileus. In twee Nederlandse ziekenhuizen werd een totaal van 53 patiënten geïncludeerd die een electieve oncologische colorectale resectie ondergingen. Uiteindelijk konden in beide behandelgroepen 20 patiënten worden geanalyseerd. Het primaire eindpunt werd gedefinieerd als de combinatie van de eerste passage van feces en het 24 uur tolereren van vast voedsel, maar er werd geen verschil tussen beide groepen gevonden. Voor nicotine en normale kauwgum was de mediane tijd tot het primaire eindpunt respectievelijk 4.5 dagen (interkwartielafstand, 3.0–7.25) vs. 3.5 dagen (3.0–4.25; $p = 0.398$). Vergelijkbaar met de primaire uitkomst, werden er ook geen verschillen gevonden in inflammatoire parameters (C-reactief eiwit, leukocyten en interleukine-6) en patiënt-gerapporteerde uitkomstmaten (e.g. pijnscores en gastro-intestinale symptomen). Het aantal postoperatieve complicaties, re-interventies en heropnames verschilde ook niet tussen beide methoden. Op basis van deze resultaten werd geconcludeerd dat in deze pilotstudie, nicotine kauwgum veilig maar ineffectief bleek voor de preventie van postoperatieve ileus en het bevorderen van het gastro-intestinale herstel.

In **Hoofdstuk 14** werden de studies in dit proefschrift bediscussieerd en werden verschillende toekomstperspectieven benoemd.



Chapter 17

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List of publications

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Dankwoord

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Beijing), Ward I of Gastrointestinal Cancer Centre, Peking University Cancer Hospital
& Institute, Beijing, China

List of Publications

Nicotine chewing gum for the prevention of postoperative ileus after colorectal surgery: a multicentre, double-blind, randomised, controlled pilot study.

Lambrichts DPV, Boersema GSA, Tas B, Wu Z, Vrijland WW, Kleinrensink GJ, Jeekel J, Lange JF, Menon AG.

International Journal of Colorectal Disease 32.9 (2017): 1267-1275.

Non-operative treatment as a strategy for patients with parastomal hernia: a multicentre, retrospective cohort study.

Kroese LF*, **Lambrichts DPV***, Jeekel J, Kleinrensink GJ, Menon AG, de Graaf EJR, Bemelman WA, Lange JF. (*Shared first authors)

Colorectal Disease 20.6 (2018): 545-551.

The Multidisciplinary Management of Acute Complicated Diverticulitis.

Lambrichts DPV, Birindelli A, Tonini V, Cirocchi R, Cervellera M, Lange JF, Bemelman WA, Di Saverio S.

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Sneiders DS, **Lambrichts DPV**, Swank HA, Blanken-Peeters CFJM, Nienhuijs SW, Govaert MJPM, Gerhards MF, Hoofwijk AGM, Bosker RJI, van der Bilt JDW, Heijnen BHM, ten Cate Hoedemaker HO, Kleinrensink GJ, Lange JF, Bemelman WA

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Multicentre study of non-surgical management of diverticulitis with abscess formation.

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On the Immune Status of Patients with Colorectal Carcinoma.

Edomskis PP, **Lambrichts DPV**, Lange JF

Emergency Surgical Management of Colorectal Cancer. Springer, Cham, 2019. 147-161.

Hartmann's procedure versus sigmoidectomy with primary anastomosis for perforated diverticulitis with purulent or faecal peritonitis (LADIES): a multicentre, parallel-group, randomised, open-label, superiority trial.

Lambrichts DPV, Vennix S, Musters GD, Mulder IM, Swank HA, (...), Vermeulen J, van Dieren S, Bemelman WA, Lange JF

The Lancet Gastroenterology & Hepatology, 4(8), 599-610.

Outcomes After Elective Colorectal Surgery by 2 Surgeons Versus 1 Surgeon in a Low-Volume Hospital.

Sparreboom CL, **Lambrichts DPV**, Menon AG, Kleinrensink GJ, Lingsma HF, Lange JF
Surgical Innovation 26.6 (2019): 753-759.

Comparison of different modalities for the diagnosis of parastomal hernia: a systematic review.

de Smet GHJ, **Lambrichts DPV**, van den Hoek S, Kroese LF, Buettner S, Menon AG, Kleinrensink GJ, Lange JF.

International Journal of Colorectal Disease, 2020, 1-14.

Sigmoid resection with primary anastomosis versus the Hartmann's procedure for perforated diverticulitis with purulent or fecal peritonitis: a systematic review and meta-analysis

Lambrichts DPV, Edomskis PP, van der Bogt RD, Kleinrensink GJ, Bemelman WA, Lange JF

International Journal of Colorectal Disease, 2020

Cost-effectiveness of sigmoid resection with primary anastomosis or end colostomy for perforated diverticulitis: an analysis of the randomized Ladies trial

Lambrichts DPV, van Dieren S, Bemelman WA, Lange JF

British Journal of Surgery, 2020

European Society of Coloproctology: guidelines for the management of diverticular disease of the colon

Schultz JK, Azhar N, Binda GA, Barbara G, Biondo S, Boermeester MA, Chabok A, Consten ECJ, van Dijk ST, Johanssen A, Kruis W, **Lambrichts DPV**, Post S, Ris F, Rockall TA, Samuelsson A, di Saverio S, Tartaglia D, Thorisson A, Winter DC, Bemelman WA, Angenete E

Colorectal Disease, 2020

PhD Portfolio

PhD Student: D.P.V. Lambrichts
 Promotores: Prof. dr. J.F. Lange
 Prof. dr. W.A. Bemelman
 Erasmus MC Department: Surgery
 PhD Period: 2015-2020

PhD Courses	Year	ECTS
Endnote	2015	1.0
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers	2015	1.5
Biomedical English Writing	2017	2.0
Research Integrity	2017	0.3
Laboratory Animal Science (Article 9)	2017	3.0
Oral presentations		
European Hernia Society, Vienna	2017	1.0
European Society for Surgical Research, Amsterdam	2017	2.0
Digestive Disease Days, Veldhoven	2018	2.0
NVvH Chirurgendagen, Veldhoven	2018	2.0
European Association of Endoscopic Surgery, London	2018	1.0
Regionale Meeting Werkgroep Coloproctologie, Rotterdam	2019	1.0
Digestive Disease Days, Veldhoven	2019	1.0
(Inter)national conferences		
Wetenschapsdag Heelkunde Erasmus MC, Rotterdam	2016	1.0
Wetenschapsdag Heelkunde Erasmus MC, Rotterdam	2017	1.0
European Society of Coloproctology, Nice	2018	1.0
European Society of Coloproctology, Vienna	2019	1.0
Teaching		
Anatomy courses for medical students	2015 – 2017	2.0
Tutor of first year medical students	2015 – 2016	1.0
Supervising Master's theses		
Master thesis Clinical Research (D. Sneiders)	2016 – 2017	1.0
Master thesis Medicine (D.C.H.E. van der Does)	2017 – 2018	1.0
Master thesis Medicine (G.H.J. de Smet)	2018 – 2019	1.0
Other		
REPAIR Research Group meetings	2015 – 2017	2.0
Masterclass 'Value-Based Healthcare', Amsterdam	2017	0.5
Member of the ESCP Diverticulitis Guideline Committee	2018 – 2020	2.0
Journal Reviewer (<i>Colorectal Disease</i>)	2019	0.5
Total		32.8

Dankwoord

Dit proefschrift had niet tot stand kunnen komen zonder de hulp van velen.

Allereerst wil ik mijn bijzondere dank uiten aan de betrokken patiënten die zich, op een kwetsbaar moment, toch bereid toonden om deel te nemen aan wetenschappelijk onderzoek.

Mijn promotor, professor Lange, ik ben u veel dank verschuldigd voor het vertrouwen dat u in mij stelde als student en voor de ruimte die u mij heeft geboden om mijzelf onder uw supervisie te ontwikkelen als onderzoeker. Niet alleen uw sturing bij de lopende projecten hebben mij veel geholpen, maar juist ook de vrijheid en steun bij het uitwerken van eigen onderzoeksvoorstellen waren erg waardevol. Uiteraard kijk ik ook met veel plezier terug op de culturele intermezzo's tijdens de REPAIR-vergaderingen.

Mijn tweede promotor, professor Bemelman, ook u ben ik veel dank verschuldigd voor het feit dat ik, met net pas mijn Bachelor op zak, de kans en het vertrouwen kreeg om coördinator van de Ladies trial te worden. Daarmee werd daadwerkelijk de kiem gelegd voor dit uiteindelijke proefschrift. Onze gesprekken hielpen mij altijd om de nodige knopen door te hakken én zorgden ervoor dat ik weer extra motivatie en nieuwe ideeën vond.

Professor Bouvy, professor van Eijck en professor Verhoef, geachte leden van de leescommissie, veel dank voor uw moeite om zitting te nemen in de leescommissie. Ook de overige leden wil ik hartelijk danken voor hun bereidheid om als opponent plaats te nemen in mijn grote commissie. Ik kijk er naar uit om met u van gedachten te wisselen tijdens de verdediging.

Professor Kleinrensink, beste prof. Als groentje mocht ik ooit starten in het Snijzaalteam, waarmee het 'academische balletje' ging rollen. Als Snijzaalteamlijert, EARP-bestuur en, uiteindelijk, promovendus: op vele manieren heb ik met u samen mogen werken en heeft u mij gestimuleerd mijzelf te ontplooien in al die verschillende rollen. Altijd was er tijd voor een goed gesprek, luisterend oor en een straffe bak koffie op de 14e verdieping. Ik heb veel bewondering voor uw tomeloze energie en positieve kijk op het leven. Quaestionem orturam iam solvimus!

Professor Jeekel, uw passie voor chirurgisch onderzoek is bewonderenswaardig en heeft mij vaak gemotiveerd. Uw nieuwsgierigheid is een voorbeeld voor alle onderzoekers.

Beste dr. Menon, beste Anand. Veel dank voor je begeleiding gedurende de uitvoering van mijn onderzoeken en de nuttige feedback op mijn manuscripten.

Beste Annelies, veel dank voor jouw waardevolle hulp bij de laatste (organisatorische) loodjes van mijn promotietraject.

Beste Susan, enorm bedankt voor je hulp bij het uitvoeren van een deel van de analyses in dit proefschrift.

Voorts mijn grote dank aan alle lokale hoofdonderzoekers, chirurgen, arts-assistenten, verpleegkundigen en secretaresses die betrokken waren bij de Ladies trial: jullie inzet en hulp waren onmisbaar!

Dan uiteraard een woord van dank aan mijn voorgangers op de Ladies trial: Hilko, Irene, Gijs en Sandra, als ook grondlegger Jeffrey Vermeulen. Met dank aan jullie eerdere inspanningen en harde werk heb ik de kans gekregen deze uitdagende studie tot een goed einde te kunnen brengen.

Beste leden van de Dutch Diverticular Disease (3D) werkgroep: prof. dr. Boermeester, prof. dr. Consten en dr. Draaisma. Het was inspirerend om deel uit te maken van dit onderzoekscollectief en te zien hoe de samenwerking heeft geleid tot het verder invullen van de hiaten binnen het diverticulitis onderzoeksveld. Hendrike, jij in het bijzonder ook bedankt voor de goede samenwerking!

Labcollegae, dank voor de onvergetelijke tijden in de kelder. Het epicentrum van de faculteit heeft veel mensen aan zich voorbij zien trekken, maar enkelen wil ik in het bijzonder bedanken. Cloë, al vanaf de eerste summer school samen opgetrokken en nu allebei een proefschrift: wie had dat gedacht!? Altijd tijd voor overleg met een 'snackerelletje', nooit te beroerd voor een fout uurtje. Leonard, dank voor de vele roestige gaten die je in mijn manuscripten hebt geschoten. Je hebt het reageren tot een kunst weten te verheffen. Michael, altijd kon ik rekenen op jouw galmende kopstemplen om de ruimte mee te vullen. Vugt, wij Brabanders weten: a worstenbroodje a day, keeps the doctor away. Yagmur, dank dat ik keer op keer welkom was in jouw hoekje van het lab, voor goed advies en/of een koffiecupje. Stefan, vele onvergetelijke uren samen doorgebracht in de krochten van het 'Ee', heel gaaf. Dank voor alle momenten van begeerten (eigenlijk voornamelijk) afleiding. Tot slot, Ron, mag jij - als pater laboratoriae - niet ontbreken in dit rijtje. Ik blijf uiteraard graag op de hoogte van je schildpadden(congres) verhalen.

Alle andere heilkunde-onderzoekers in Rotterdam en Amsterdam met wie ik paden heb gekruist in de afgelopen jaren: dank voor alle mooie momenten!

Chirurgen en assistenten uit het Maasstad Ziekenhuis: dank voor de mooie en leerzame tijd tot nu toe!

Roosendalers, ook zoveel jaren nadat we het Gertrudis achter ons hebben gelaten, zijn we elkaar nog niet uit het oog verloren. Over het land uitgewaaid, maar altijd genoeg reden om samen te komen voor een Bourgondische borrel. De Derde Kerstdag staat alvast weer gereserveerd.

Huize Volmarijn, lieve Tho, Jeff, Daaf, Lien, Yv en Saar. Ik had me geen betere huisgenoten kunnen wensen. De herinneringen zijn schitterend en ontelbaar. Het is mooi om te zien hoe jullie allemaal jullie eigen doelen en dromen nastreven.

Boris, goede vriend. Altijd bomvol mooie verhalen. Het is goed om te weten altijd het leven met je te kunnen bespiegelen (in aanwezigheid van een goed glas). Sjoerd, buurman, wanneer gaan we varen? Galjart, monsieur, binnenkort dan maar weer eens met het Moksi-peloton op pad.

Mijn paranimfen, Ruben en Gijs. Niet alleen wetenschappelijk zijn wij een succesvol team gebleken, maar ook als belangrijke sfermakers in Vakje E hebben wij onze strepen ruimschoots verdiend. Het is een bijzonder genoegen dat jullie aan mijn zijde staan tijdens mijn verdediging.

Lieve Rob, Birgit, John, Jeffrey, Kim, Bobbi en Mikkie. Dank voor jullie warmte en interesse. Ik kan me geen fijnere schoonfamilie bedenken.

Dear JoAnne, although often from distant places around the globe, thank you for your support and interest.

Lieve oma, wellicht vind ik ooit nog die wonderpil voor je uit. In de tussentijd is dit toch ook al een aardige pil geworden.

Lieve Claire, grote zus, ik ben onwijs trots op je.

Lieve mam, lieve pap, voor altijd ben ik jullie dankbaar voor jullie onvoorwaardelijke steun en liefde.

Lieve Isabel, lief, dank voor alles. Ik kan niet wachten om de wereld met je te ontdekken.

Curriculum Vitae

Daniël Peter Valentin Lambrichts was born in Brunssum (the Netherlands) on the 25th of September 1992. He grew up in Roosendaal (the Netherlands) and graduated from the Gertrudiscollege (VWO Gymnasium). In 2011, he started medical school at the Erasmus University Medical Center in Rotterdam (the Netherlands). During his study, he became a member of the student team at the Cadaver Lab (Department of Anatomy and Neuroscience), where he got involved in the peer-to-peer Erasmus Anatomy Research Project as a student, as well as a tutor and board member. After obtaining his Bachelor's degree in 2014, he started his research master in Clinical Research (Netherlands Institute for Health Sciences) during which he attended the Summer Institute of Epidemiology and Biostatistics at the Johns Hopkins Bloomberg School of Public Health (Baltimore, United States). In 2015, he joined the REPAIR Research Group (supervisors: prof. dr. J.F. Lange, prof. G.J. Kleinrensink, prof. dr. J. Jeekel, and dr. A.G. Menon) as part of his research master, where he started his research into the management of complicated diverticulitis. The present thesis is the result of the PhD project that he subsequently worked on under the supervision of prof. dr. J.F. Lange (Erasmus MC) and prof. dr. W.A. Bemelman (Amsterdam UMC, AMC). In November 2017, he commenced with his Master's program in Medicine, while finishing his research and thesis. After receiving his Master's degrees in Medicine and Clinical Research in April and May 2020, he started working as resident (not in training) at the Department of Surgery of the Maastad Hospital (Rotterdam).

The first part of the paper discusses the importance of understanding the cultural context of the research. It highlights the need for researchers to be sensitive to the values and beliefs of the communities they are studying. This is particularly important in the field of education, where cultural differences can significantly impact learning outcomes. The paper then moves on to discuss the challenges of conducting research in culturally diverse settings. It notes that researchers often face difficulties in establishing rapport with participants and in interpreting their responses. To address these challenges, the paper suggests several strategies, including the use of local informants and the development of culturally appropriate research instruments. The final part of the paper discusses the importance of ethical considerations in cross-cultural research. It emphasizes the need for researchers to obtain informed consent from participants and to ensure that their research does not cause harm to the communities they are studying.

In conclusion, the paper argues that a deep understanding of the cultural context is essential for conducting effective research in education. It calls for researchers to adopt a more holistic and culturally sensitive approach to their work. By doing so, they can better understand the needs and experiences of the communities they are studying and develop more effective educational interventions. The paper also highlights the importance of ethical considerations in cross-cultural research and calls for researchers to be transparent and accountable in their work.